Cannabis and Psychosis

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Alberta Health Services
Alberta Addiction and Mental Health Research Partnership Program

Declaration of Interests (*none* with any relationship to work presented)

Prior to 2011

- **Research grants:**
  - **Bristol-Myers Squibb and Otsuka Pharmaceuticals Limited; Johnson & Johnson Pharmaceutical Research and Development**
- **Research partnerships:**
  - **GlaxoSmithKline**
- **Invited member of Advisory Boards:**
  - **Johnson & Johnson, Lundbeck, Roche Diagnostics, and Bristol- Myers Squibb and Otsuka Pharmaceuticals Limited**
- **Consultancy fees:**
  - **Bristol-Myers Squibb, Lundbeck, Roche Molecular Systems, Roche Diagnostics, Johnson & Johnson Pharmaceutical Research and Development**
- **Consultancy fees and research support:**
  - **Roche Diagnostics and Roche Molecular Systems**

2017

- **Consultancy for Otsuka Canada Pharmaceutical Inc., Lundbeck Canada, and HLS Therapeutics**
- **Research grant from Jannsen Inc., Canada (fellowship for a trainee)**

Disclosures

- **Member, Schizophrenia Society of Alberta**
- **Member, Alberta Cannabis Research and Innovation Network**

Mitigating Potential Bias

No commercial funding for the work to be presented, and conducted prior to the setting up of the Alberta Cannabis Research and Innovation Network

Conducted according to scientific rigour and published in peer-reviewed journals (Lodhi et al., 2017; Tibbo et al., 2017)

Learning Objectives

1. Specify by how much cannabis increases the risk of becoming psychotic
2. Identify risk factors for psychosis after cannabis consumption
3. Identify a gene associated with psychosis after cannabis consumption

Findings from 2015 Canadian Tobacco, Alcohol and Drugs Survey (CTADS)

Cannabis was the most commonly used illicit drug and prevalence was 12% (3.6 million people)

Age	Prevalence of cannabis use (CTADS, 2015)
15-19 years	21% (426,000)
20-24 years old	30% (715,000)
25 years or older	10% (2,500,000)

- Males (15%) use more than Females (10%), although there has been an increase in the amount females use since 2013
- Median Age of first use is 17 years
- Among adults aged 25 and older, use increased from 8% in 2013 to 10% in 2015

2015 Canadian Tobacco, Alcohol and Drugs Survey (CTADS, cont'd)

Among past-year cannabis users:

72%	reported using cannabis in the **past 3 months** (2.6 million people)
33%	reported using cannabis on a **daily basis** (840,000 people)
24%	reported using cannabis for **medical purposes** (831,000 people)
28%	reported using a **vapourizer** to consume cannabis (999,000 people)

Percentage of cannabis use

	Lifetime	Annual
Grade 8	5.70%	4.40%
Grade 9	16.70%	14.00%
Grade 10	26.70%	23.00%
Grade 11	35.00%	27.10%
Grade 12	39.80%	30.30%

The Alberta Youth Experience Survey, Technical Report, 2008 (N=3,469)

While adolescent cigarette (tobacco) smoking is reducing, young people perceive cannabis as *less harmful than cigarettes* (Berg et al, 2015)

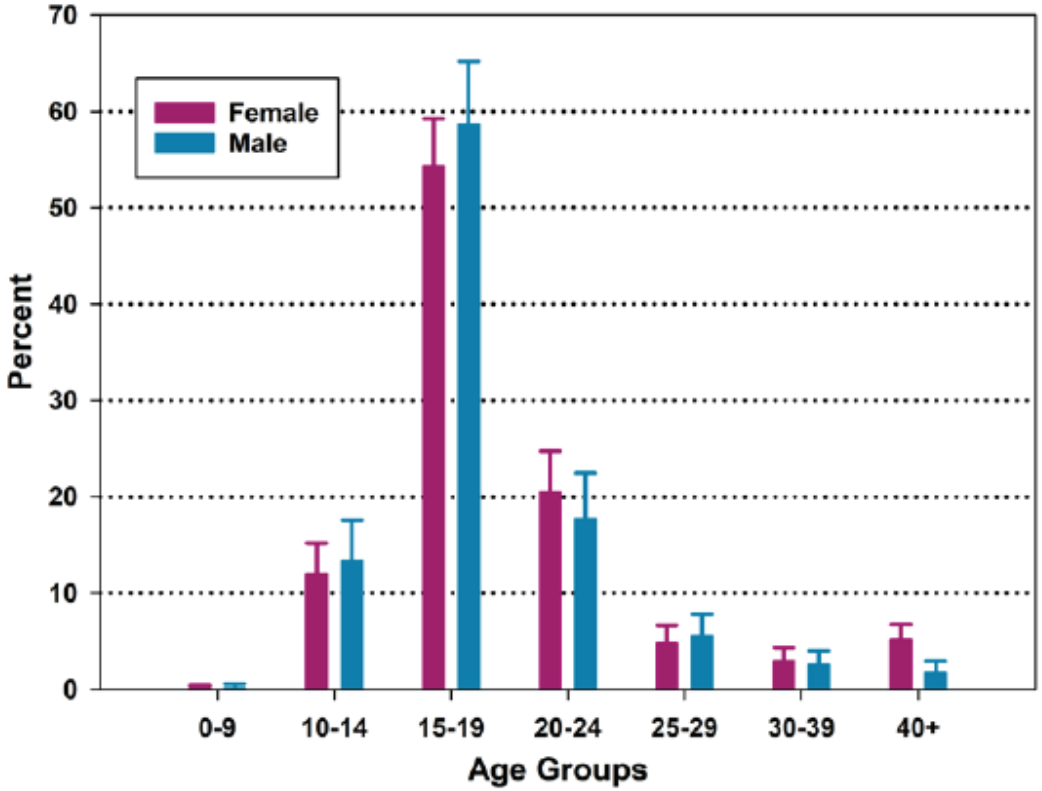
Young people are *more likely than older* individuals to view cannabis use as having *few risks* (Pacek et al, 2015)

Health Trends Alberta

October 16, 2018

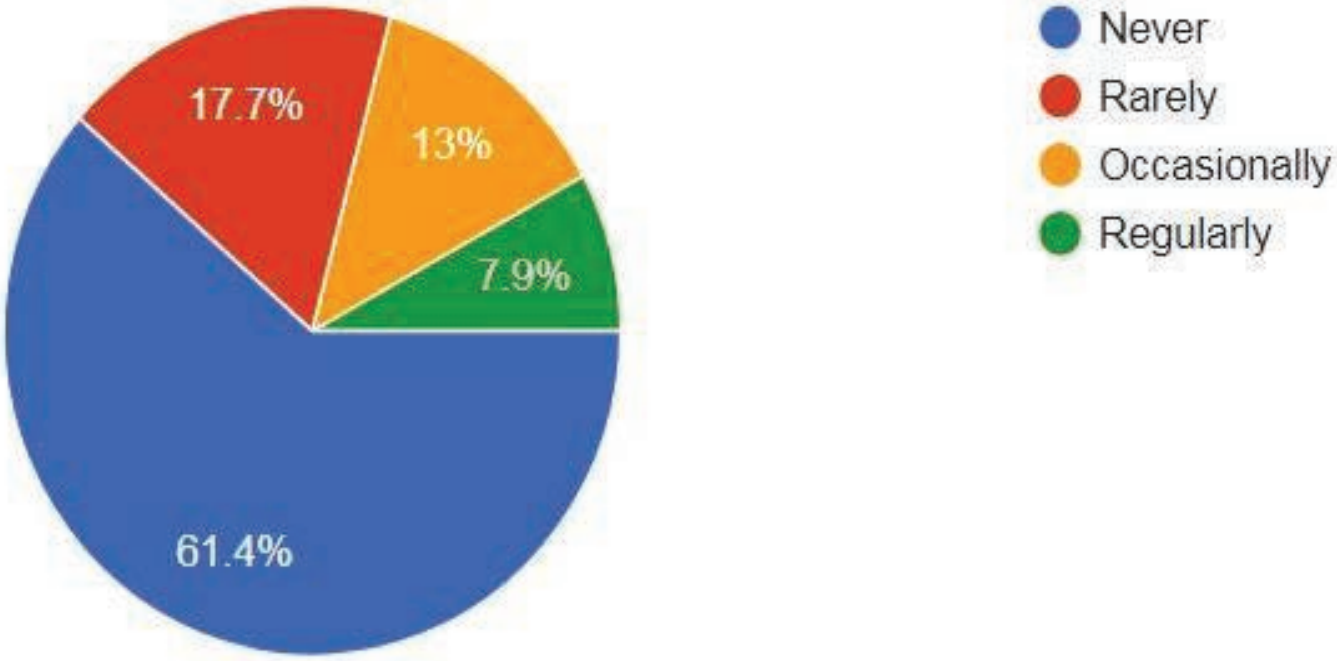
Alberta-based data on cannabis use was collected via the 2017-18 Alberta Community Health Survey (ACHS). It comprised a telephone/web survey of approximately 6,500 Albertans 18 years and older. They found:

- Median age for first use of cannabis was **17 years old**
- **48%** reported using cannabis at least once in their life
- **88%** started between the ages of **10 and 24** years old
- **57%** started between the ages of **15 and 19** years old
- There were **no gender/sex differences for age of onset** except in the 40+ group when more females started



How often do you currently use cannabis?

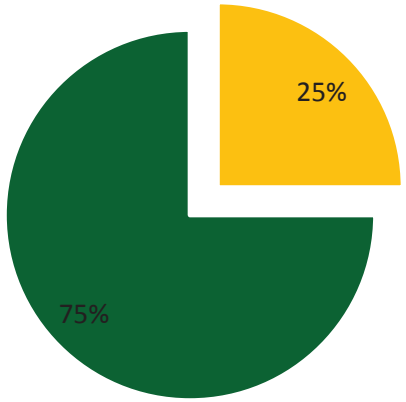
2,596 responses



From the University of Alberta Community Survey on Cannabis

25% of participants have used cannabis in the past year

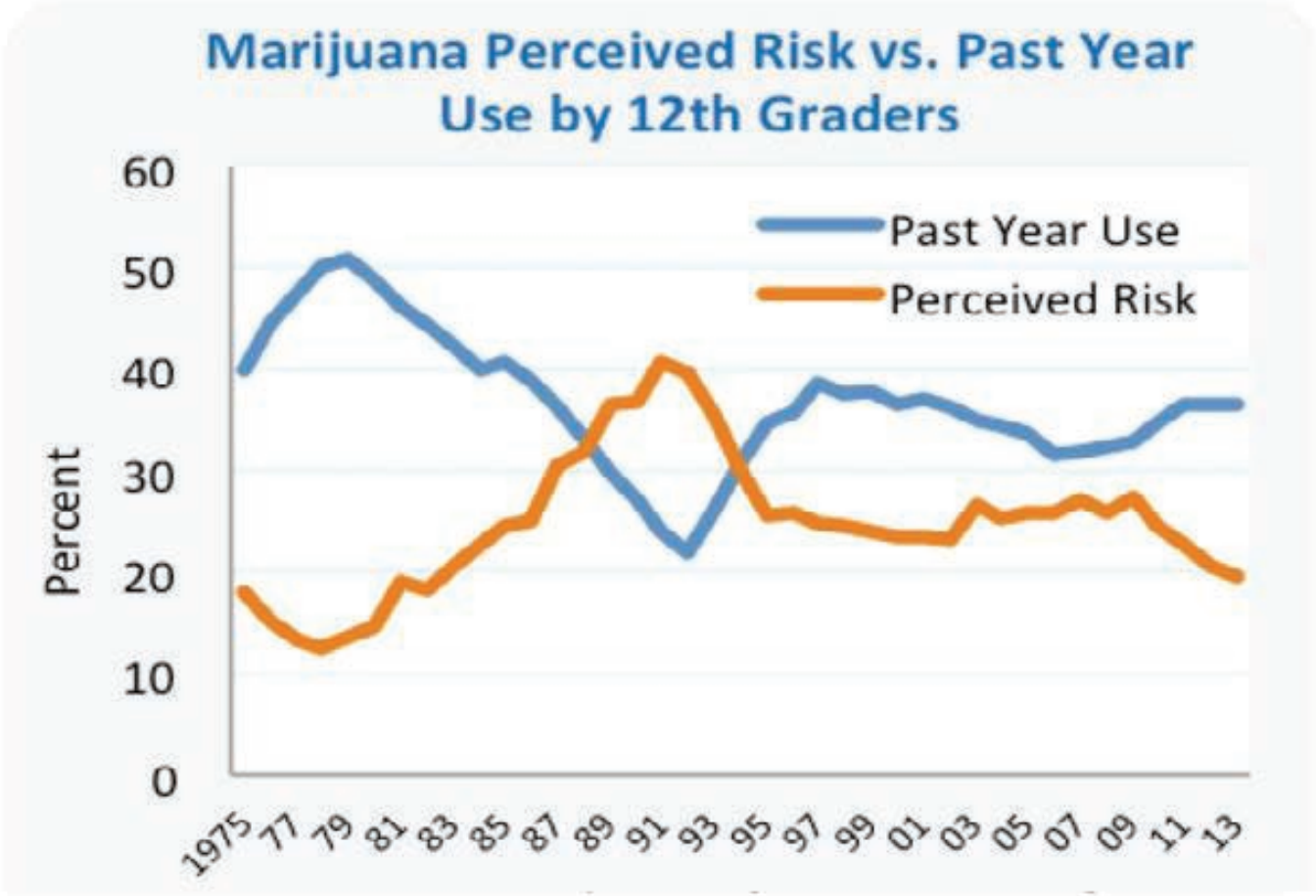
445 responses from University of Alberta students



11% of the 25% have cannabis use disorder = 2.75%

Aitchison lab unpublished data

"Young people are showing less disapproval of marijuana use and decreased perception that marijuana is dangerous"

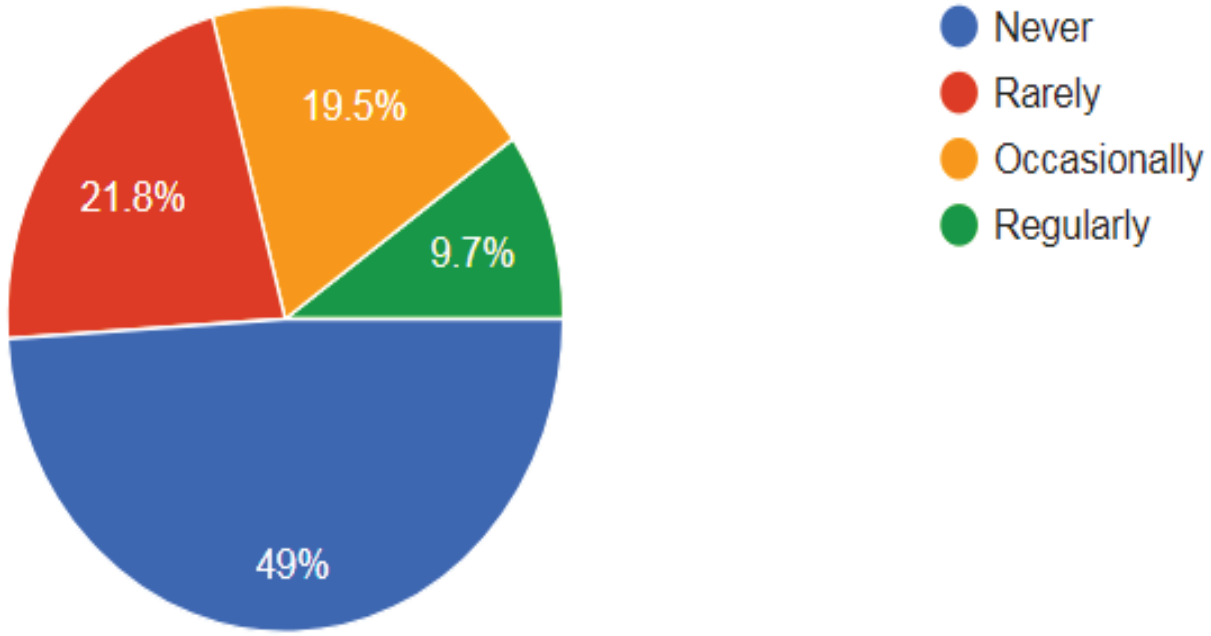


Volkow *et al*., 2014

Students

How often are you likely to use legal cannabis?

2,598 responses



From the University of Alberta Community Survey on Cannabis

Addictive Potential of Cannabis

Cannabis dependence is in fact the most common type of drug dependence after alcohol and tobacco in Canada, Australia, and the U.S.[1]

An epidemiological survey in the U.S. estimated the cumulative lifetime probability of transition to dependence was 8.9%, with half of the transitions being observed approximately 5 years after first use[2,3]

8.9% Cumulative lifetime risk of transition to dependence on cannabis

With those at least 45 years as the reference category, the odds ratio (OR) for cannabis dependence was 5.37 (95% CI 3.9-7.4) for those 18-29 years. and 2.67 (95% CI 2.0-3.6) for those 30-44 years[2,3]

- % increase in risk of becoming dependent on cannabis for those 18-29 y compared to at least 45 y = ((5.37-1)/1)*100 = 437%

Early onset of use (before age 14 years) was also associated with an increased risk of cannabis dependence (OR 2.57, 95% CI 2.0-3.1)[2,3]

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[1]Hall, W. and R.L. Pacula, *Cannabis use and dependence : public health and public policy*. 2003, Cambridge, UK ; New York, NY: Cambridge University Press. xiv, 298
[2]Anthony, J.C., *The epidemiology of cannabis dependence*. Vol. 9780521814478. 2006. 58-105.
[3]Lopez-Quintero, C., et al., *Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).* Drug Alcohol Depend, 2011. **115**(1-2): p. 120-30.

KNOW WHAT YOU ARE GETTING

AVOID INHALING TOO DEEPLY

CANNABIS CAN BE CONSUMED IN DIFFERENT FORMS

DON'T USE SYNTHETIC CANNABIS

IF USING, CONSIDER NON-SMOKING METHODS

ASK ABOUT POTENCY

CHOOSE CANNABIS WITH LOWER THC LEVELS

THC
gives you the high

Cannabis with high THC content can result in significantly worse mental health and cognitive outcomes[2]

THC CBD

CBD
can have benefits

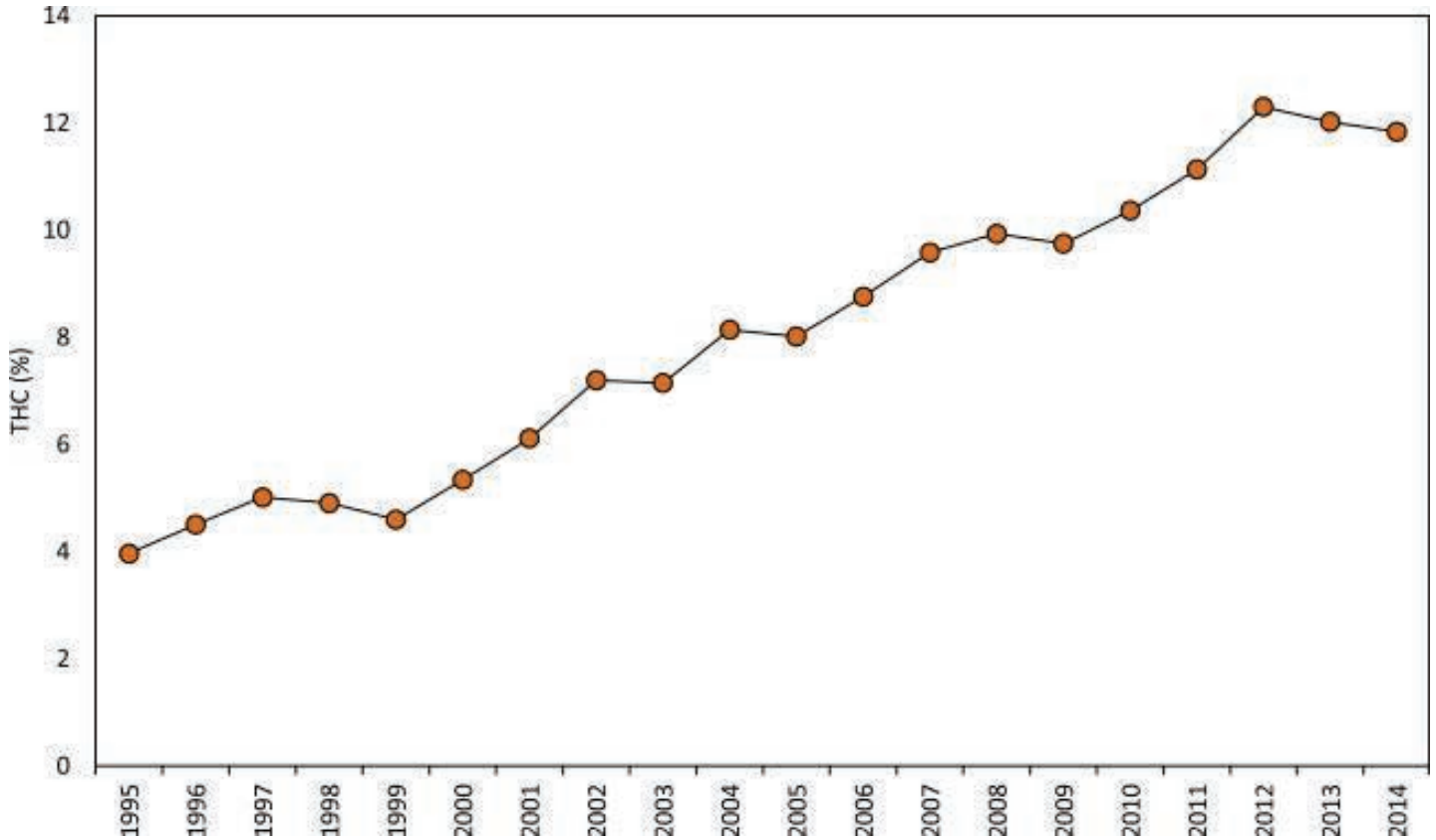
Cannabidiol (CBD) is the main non-psychotropic component in cannabis

CBD is found to have a small, but significant relationship to self-reported positive symptoms. The therapeutic properties of CBD are reduced when the cannabis is smoked.[3,4]

2. Tibbo P, *et al.* Implications of Cannabis Legalization on Youth and Young Adults. *Can J Psychiatry.* 2018;63(1):65-71.
3. Marco EM, *et al.* Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects. *Front Behav Neurosci.* 2011;5:63.
4. Schubart CD, *et al.* Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res.* 2011;130(1-3):216-221.

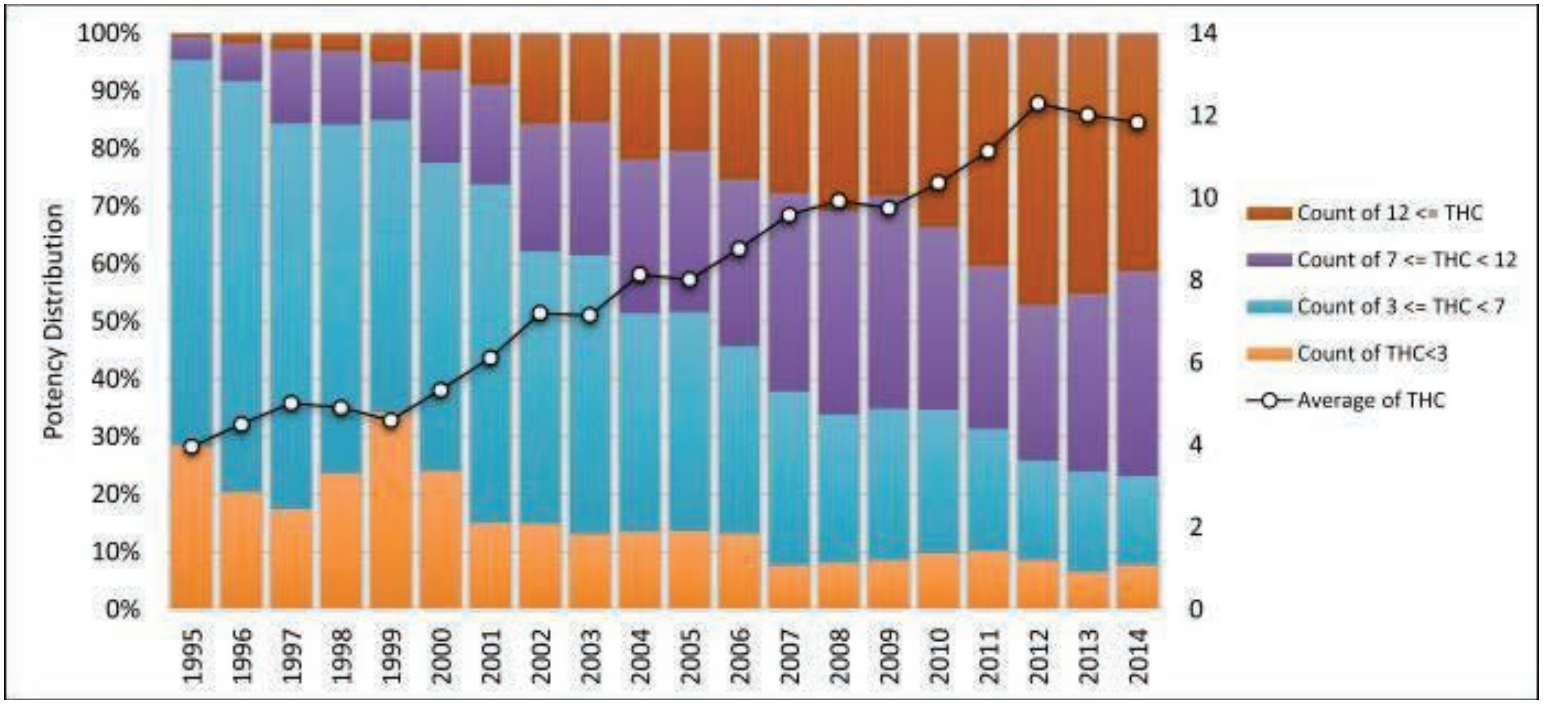
Images from: Canadian Consortium for Early Intervention Psychosis (CCEIP) Cannabis Use Tear-Pad (EN, 2018) help4psychosis.ca/wp-content/uploads/2018/05/2018-CCEIP-Cannabis-Tear-Pad-EN-pdf.pdf, or mycannabisiq.ca/portfolio/cceip-cannabis-use-tear-pad-en-2018/

Average Δ^9-tetrahydrocannabinol (Δ^9-THC) concentration of U.S. drug and enforcement administration (DEA) specimens



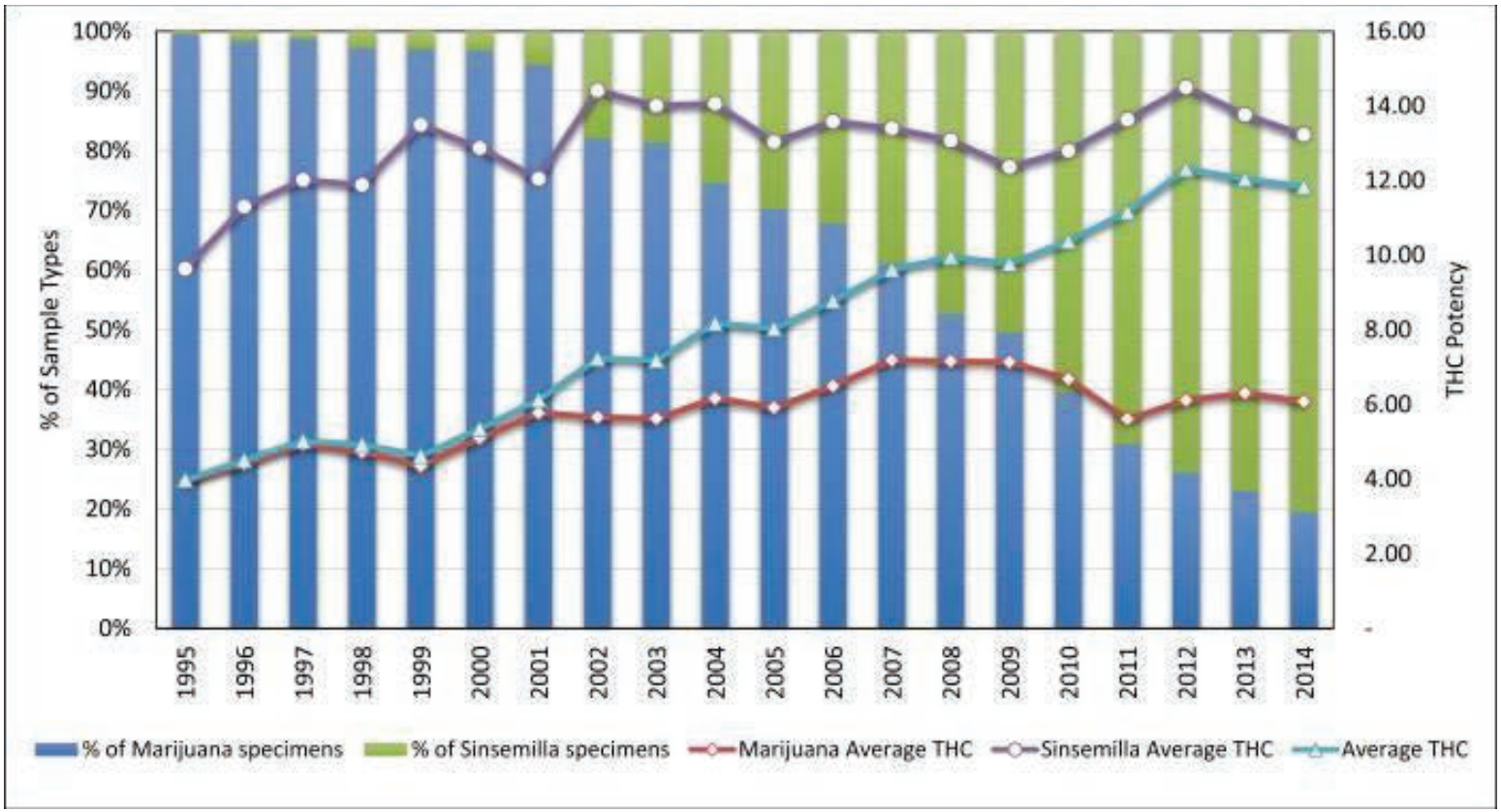
El-Sohly et al. *Biol Psychiatry*, 2016. doi: 10.1016/j.biopsych.2016.01.004

THC potency distribution of cannabis samples from DEA specimens and average annual THC



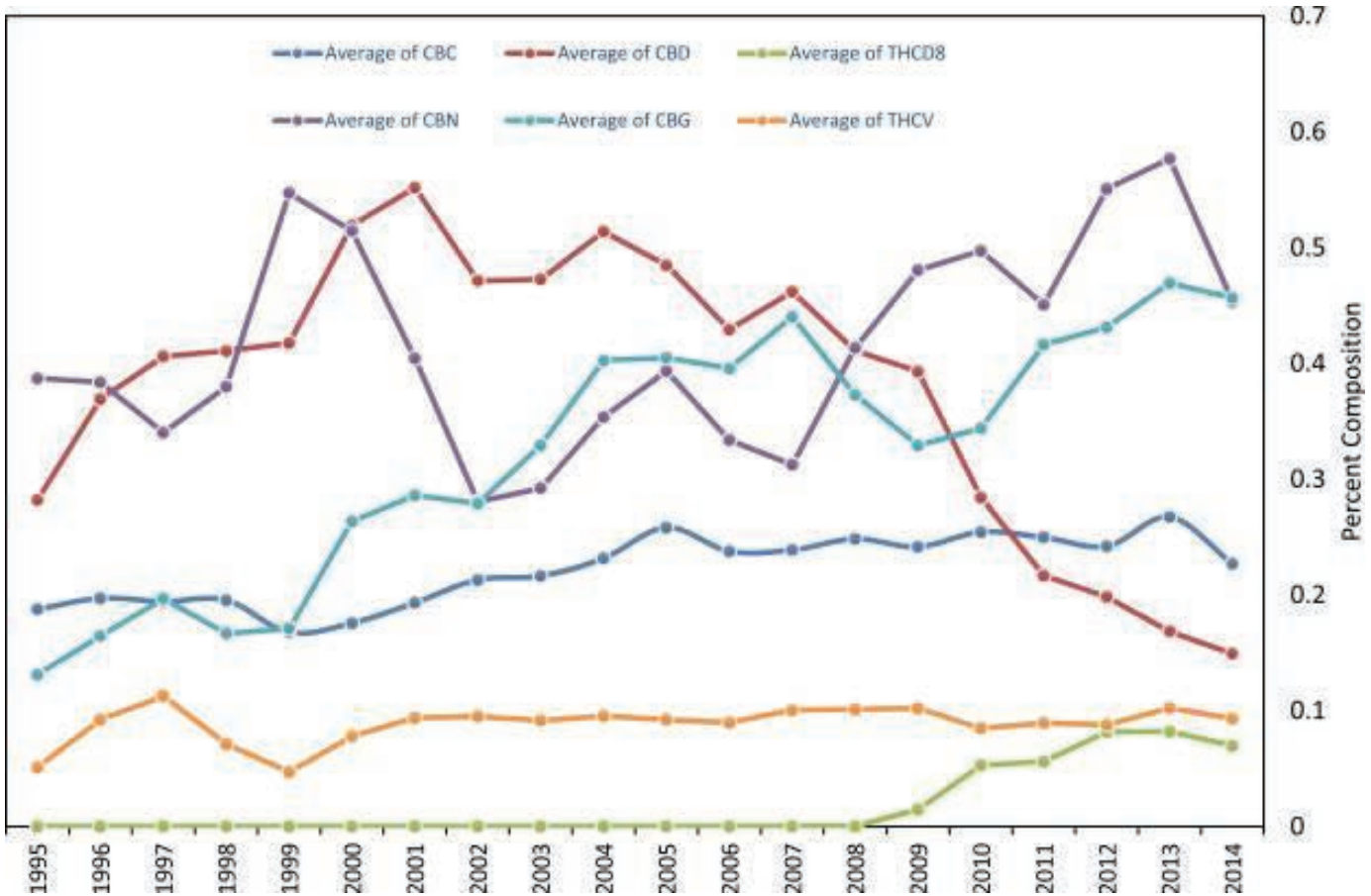
El-Sohly et al. *Biol Psychiatry*, 2016

Comparison of marijuana and sinsemilla samples confiscated by DEA



El-Sohly et al. *Biol Psychiatry*, 2016

Average concentration of Cannabichromen (CBC), Cannabidiol (CBD), Δ^{8}-Tetrahydrocannabinol (Δ^{8}-THC), Cannabinol (CBN), Cannabigerol (CBG), Tetrahydrocannabivarin (THCV), in DEA specimens (All cannabinoids except Δ^{9}-THC)



El-Sohly et al. *Biol Psychiatry*, 2016

Cannabis and psychosis

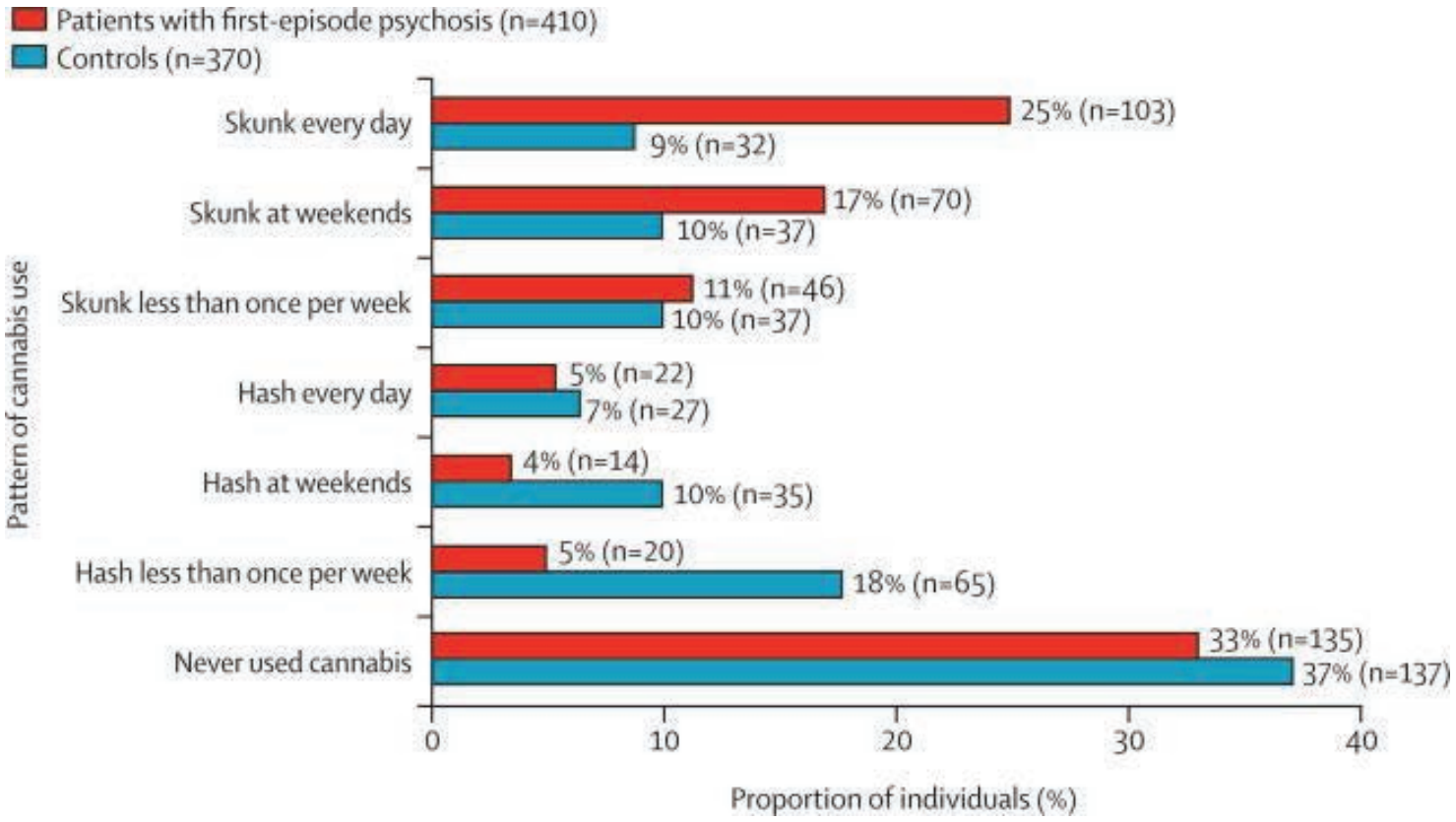
Cannabis use increases the risk of experiencing psychotic symptoms by 40% (Moore, T.H.M., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., & Lewis, G. (2007). *Lancet* 370, 319–328.)

The evidence is strong enough to warrant a public health message that cannabis use can increase the risk of psychotic disorders

However, further studies recommended, including those aiming to identify high-risk groups particularly susceptible to the effects of cannabis on psychosis

(Gage SH, Hickman M, Zammit S. (2016). Biol Psychiatry. 2016;79(7):549-56.)

Patients with first episode psychosis use cannabis more than controls



What affects risk of psychosis after cannabis consumption?

- **Age of first use of cannabis**
- **Age of regular use of cannabis**
- **Frequency of cannabis use**
- **Potency of cannabis**
- **Childhood trauma**
  - Particularly sexual abuse
- **Genes**

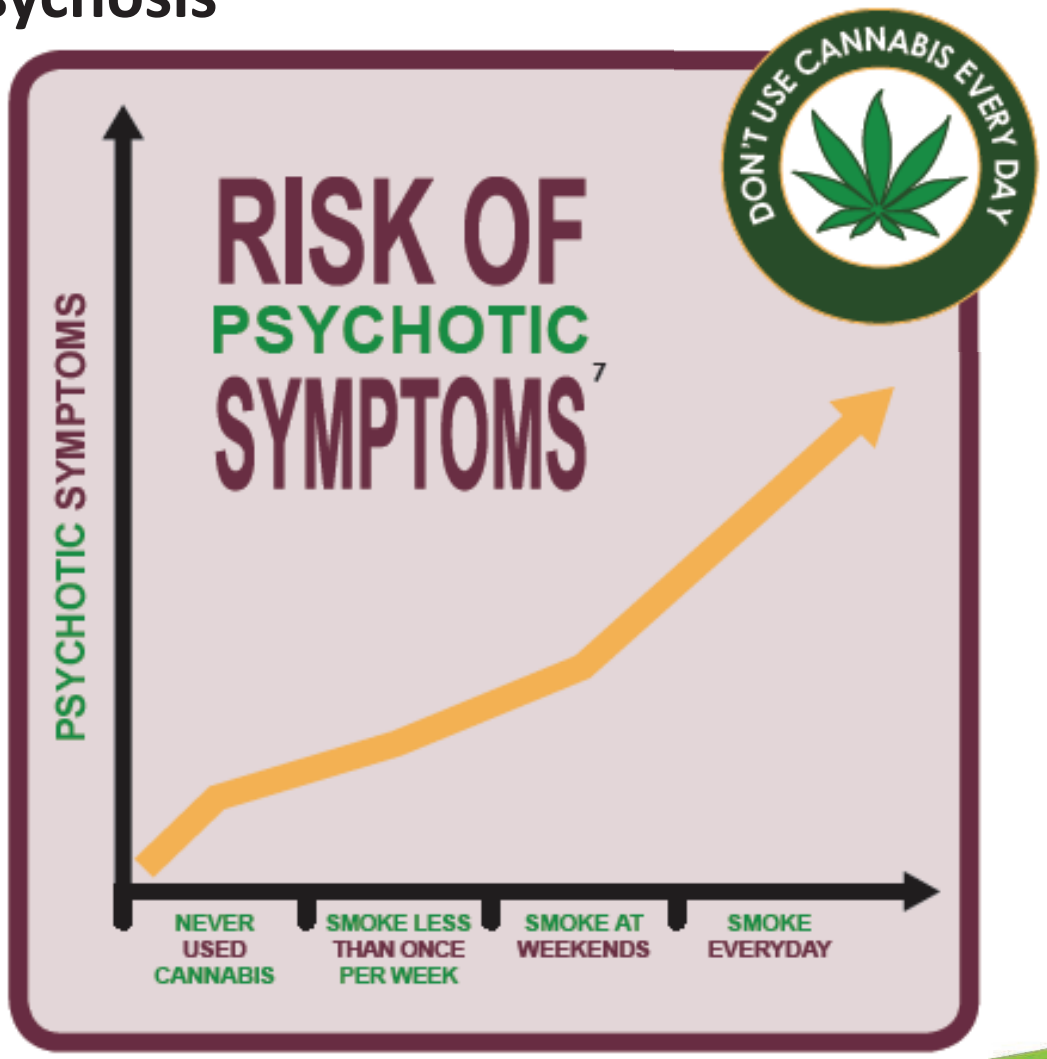
And the factors above may interact with each other

Stefanis *et al*., 2007; Ira *et al*., 2014; Alemany *et al*., 2014

Effects of Cannabis on Psychosis

Risk of psychotic symptoms increases with frequency at which cannabis is consumed

It is suggested that those who use cannabis avoid using it every day



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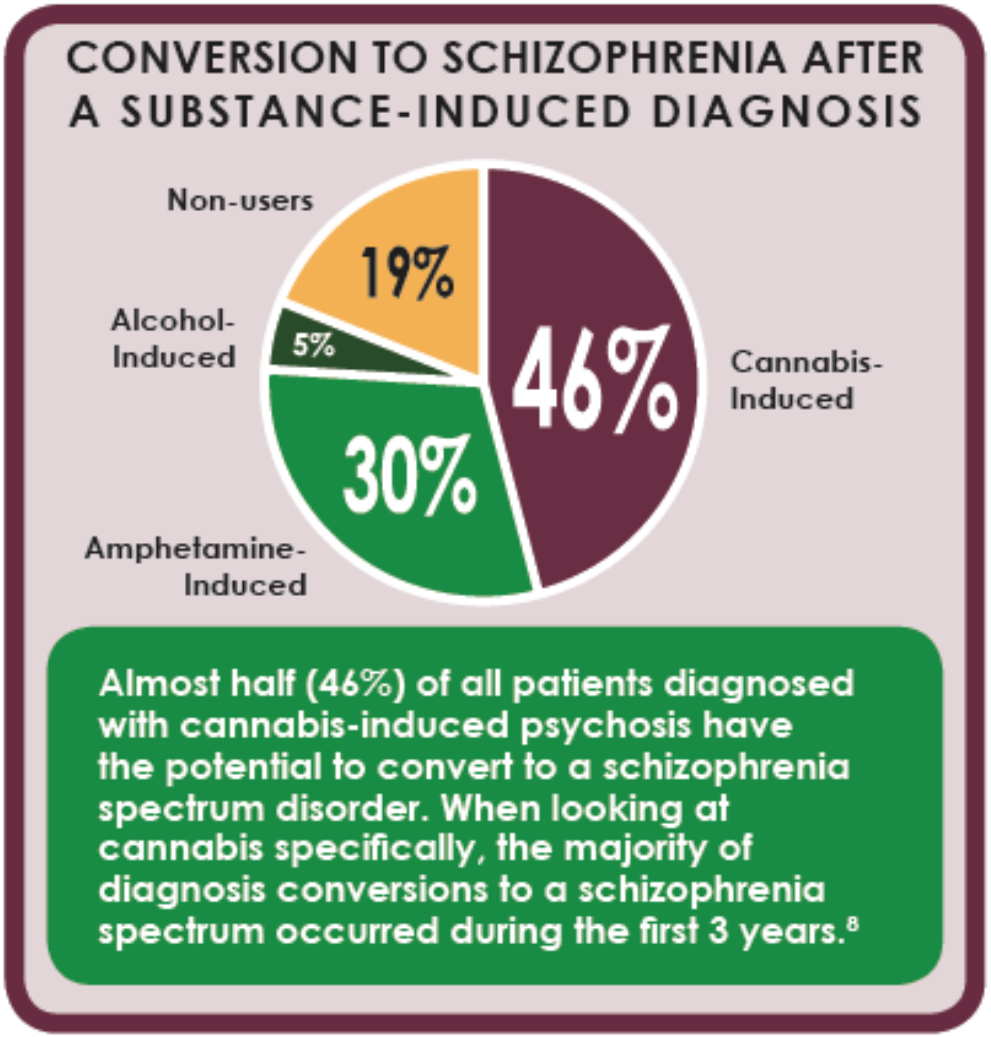
Nearly 50% of cannabis-induced psychosis converts to a schizophrenia type of illness



Niemi-Pynttäri JA, *et al. (2013)* Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. *J Clin Psychiatry,* 74(1):e94-99.

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Childhood Trauma and Cannabis Use

Childhood trauma and cannabis use are both implicated as environmental factors that contribute to psychosis

Table 4. Transition as a function of proxy environmental and genetic exposures.

		Non-transition		Transition		Odds ratio$_{adj}$*	95% CI	PAF #
		n	%	n	%			
Minority position	Majority	1,117	88.5	7	63.6	3.8	1.2–12.8	28%
	Minority	145	11.5	4	36.4			
Urban birth	Non-urban	807	68.0	3	32.0	3.7	0.9–15.4	45%
	Urban	379	37.5	5	62.5			
Cannabis use	No use	798	63.2	3	27.3	4.1	1.1–15.4	57%
	Use	464	36.8	8	72.7			
Early trauma	No	921	78.9	1	11.1	34.4	4.4–267.4	86%
	Yes	247	21.2	8	88.9			
Any exposure	No	447	35.4	0	0.0	∞		
	Yes	815	64.6	11	100.0			
High risk group	Comparison subject	460	99.6	2	0.4	2.2	0.5–10.3	50%
	Sibling	802	98.9	9	1.1			

*Odd ratio's adjusted for age sex and high-risk sibling status.
PAF = population attributable fraction, or the reduction in incidence that would be observed if the population were entirely unexposed, compared with its current exposure pattern.
∞ = OR is infinity due to zero denominator.
doi:10.1371/journal.pone.0076690.t004

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van Nierop M, Janssens M, Genetic Risk OUtcome of Psychosis (GROUP) Investigators, Bruggeman R, Cahn W, et al. (2013) Evidence That Transition from Health to Psychotic Disorder Can Be Traced to Semi-Ubiquitous Environmental Effects Operating against Background Genetic Risk. PLOS ONE 8(11): e76690. https://doi.org/10.1371/journal.pone.0076690
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0076690

Childhood Trauma, Cannabis Use and Psychosis

Some studies suggest that cannabis use and childhood trauma may interact and increase the Odds Ratio (OR) of onset of psychosis (Houston et al. 2008; Shevlin et al. 2009).

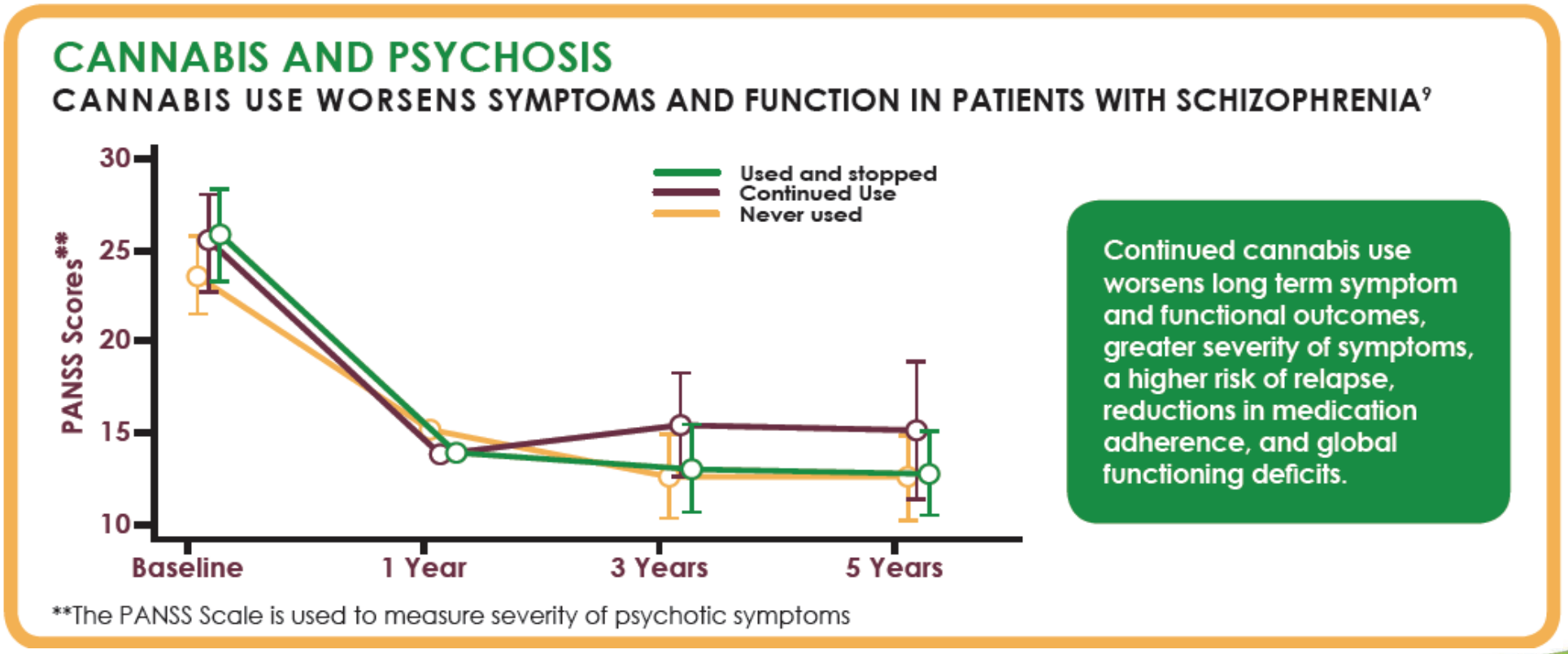
		Odds Ratio	p-value (significance)
trauma exposure only (sexual abuse)		2.45	<0.05
cannabis use and trauma exposure	cannabis use **before** trauma	4.39	<0.05
	trauma **before** cannabis use	4.25	<0.05

Shevlin et al., 2009

Childhood trauma may also be associated with cannabis use. Therefore adverse experiences in childhood may be an extraneous and/or mediating factor between cannabis use and onset of psychosis (Houston et al. 2011)

Effects of Cannabis on Psychosis

Cannabis use can worsen the course of illness in psychosis



González-Pinto A, *et al.* Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use. *Schizophr Bull.* 2011;37(3):631-639.

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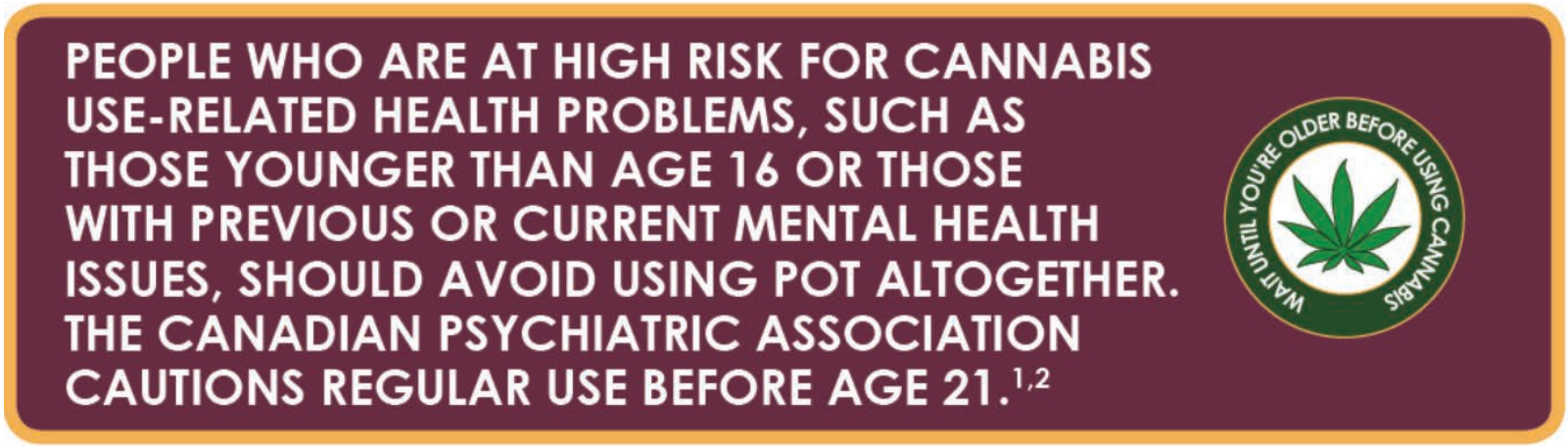
Age of first usage of cannabis: what age counts?

- **In those first using cannabis by age 15 - the Odds Ratio (OR) of experiencing psychosis increases to 4.50 (CI 1.11-18.21)**
- **In those first using cannabis by age 18 - the OR increases to 1.65 (CI 0.65-4.18)**
- **Although the ORs are different, the wide and overlapping confidence intervals indicate that *the risk of psychosis is similar in the two age groups***



1. Fischer B, *et al.* Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations. *Am J Public Health.* 2017;107(8):e1-e12.
2. Tibbo P, *et al.* Implications of Cannabis Legalization on Youth and Young Adults. *Can J Psychiatry.* 2018;63(1):65-71.

Arseneault *et al.*, BMJ, 2002

Genetic Evidence

➢ Catechol-*O*-methyltransferase (*COMT*)

- One of the major degradative pathways for:
  - Catecholamine transmitters (DA, ADR, NA); for DA especially PFC

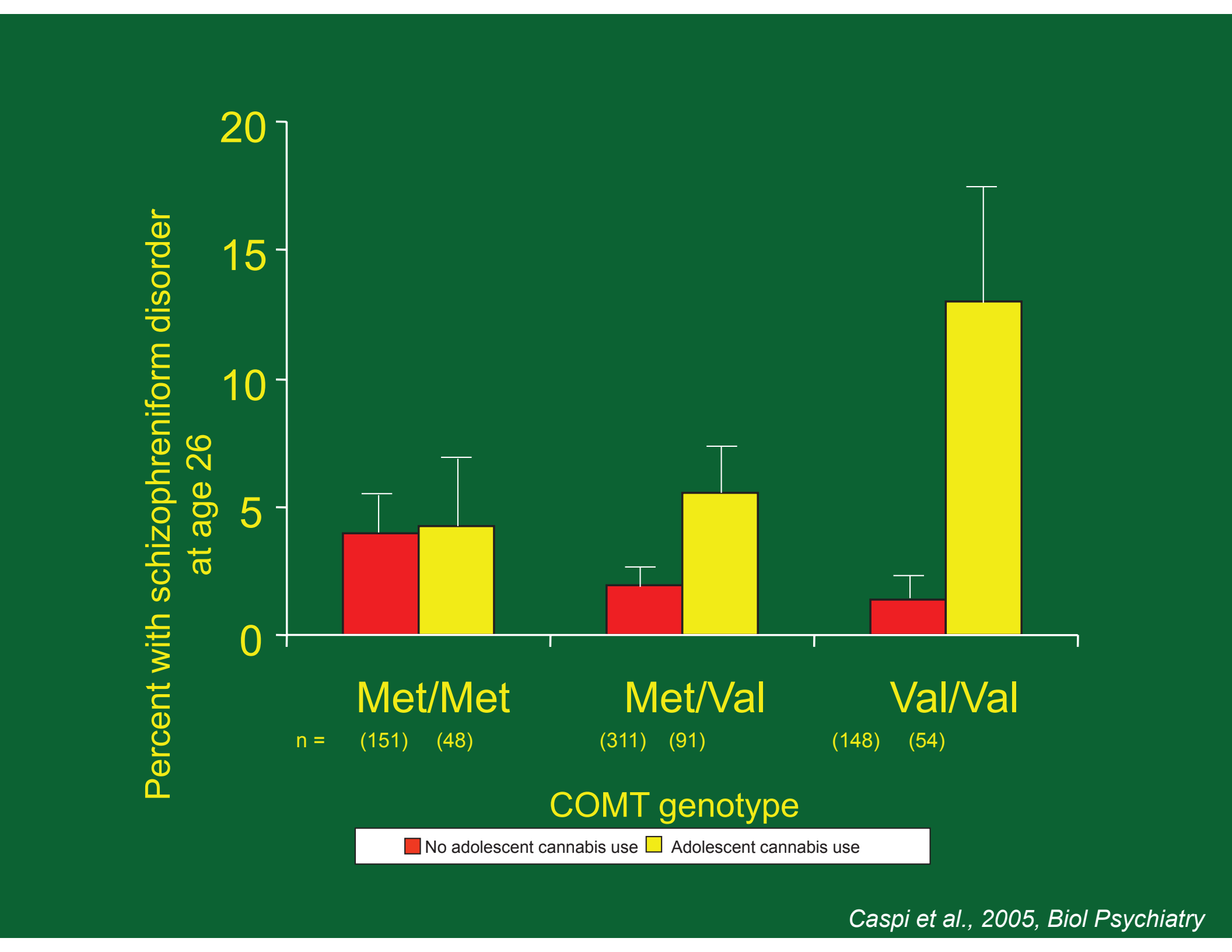
- COMT enzyme activity
  - Trimodal distribution: low / intermediate / high
  - 3- to 4-fold difference in activity between the extremes
  - Associated with rs4680 genetic variant (G>A substitution), results in a valine to methionine substitution
    - Met/Met low activity, Val/Met intermediate, Val/Val high

COMT and cannabis

- COMT plays a key role in the metabolism of monoamines, including dopamine in the prefrontal cortex (an area particularly relevant to schizophrenia)

- There is a genetic variant in this enzyme, whereby the substitution of one single letter in the "genetic code" or "DNA" (G to A) is associated with a change in the protein sequence (one "building block" of the protein - an amino acid valine is changed to another one, methionine), which is associated with a three- to four-fold change in activity of the enzyme
  - Val/Val is the high activity, Met/Met low activity, and Val/Met in between

- Caspi *et al.* (2005) reported an association between the *COMT* Val158Met variant and schizophreniform disorder at age 26 years
  - Val carriers had a 10-fold increased risk (OR 10.9, CI 2.2-54.1) if they used cannabis during adolescence
    - Defined as first use before age 15 years or monthly use before 18 years
  - Individuals that had one copy of the Val had a two and a half-fold increased risk (OR 1.5, CI 0.78-8.2)



Caspi et al., 2005, Biol Psychiatry

PLOS ONE

RESEARCH ARTICLE

The interaction between cannabis use and the Val158Met polymorphism of the COMT gene in psychosis: A transdiagnostic meta – analysis

Thomas Stephanus Johannes Vaessen[1☯], Lea de Jong[1☯], Annika Theresia Schäfer[1], Thomas Damen[1], Aniek Uittenboogaard[1], Pauline Krolinski[1], Chinyere Vicky Nwosu[1], Florentina Maria Egidius Pinckaers[1], Iris Leah Marije Rotee[1], Antonius Petrus Wilhelmus Smeets[1], Ayşegül Ermiş[2], James L. Kennedy[3], Dorien H. Nieman[4], Arun Tiwari[3], Jim van Os[5,6,7], Marjan Drukker[5]*

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Vaessen et al., 2018, PLoS One.

In case-only studies, the interaction between cannabis use and COMTVal158Met was statistically significant. When omitting all studies one by one, the OR varied between 1.24 and 1.67 and in 3 instances, the OR was no longer statistically significant

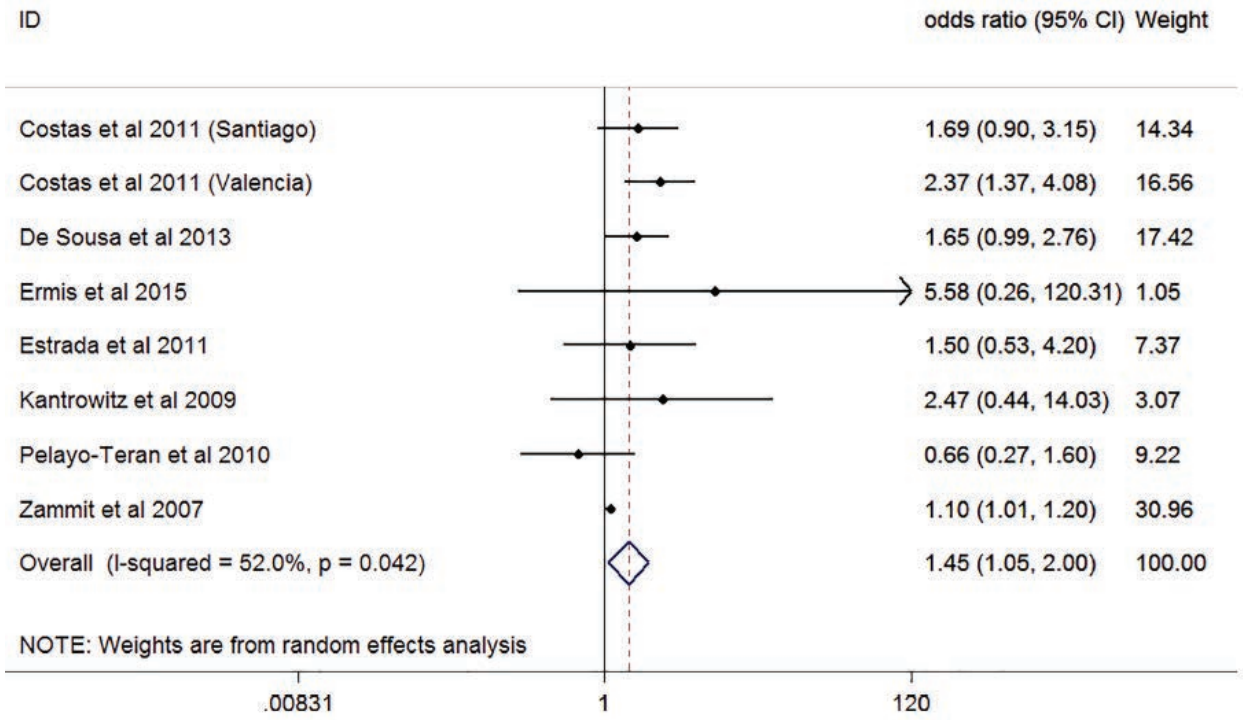

Fig 2. Forest plot case-only studies (figure shows odds ratios; random effects).

Vaessen et al., 2018, PLoS One.

However

The meta-analysis did not include the data of Lodhi et al., 2017

Investigation of the *COMT* Val158Met variant association with age of onset of psychosis, adjusting for cannabis use

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Lodhi et al. (Nov 2017), Brain and Behaviour, 7(11): e00850. DOI: 10.1002/brb3.850
Freely downloadable at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5698868/pdf/BRB3-7-e00850.pdf

Methods

Patients recruited from two first episode psychosis teams in Edmonton and Halifax, and via local collaborators:

- Alberta Hospital Edmonton & Halifax community mental health teams

Diagnoses:

- Schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic episode, psychosis NOS, and substance-induced psychosis

Data on cannabis use collected using a self-rated computerized questionnaire (Purdon, 2007)

Genotyping

DNA was extracted from saliva collected using Oragene kits

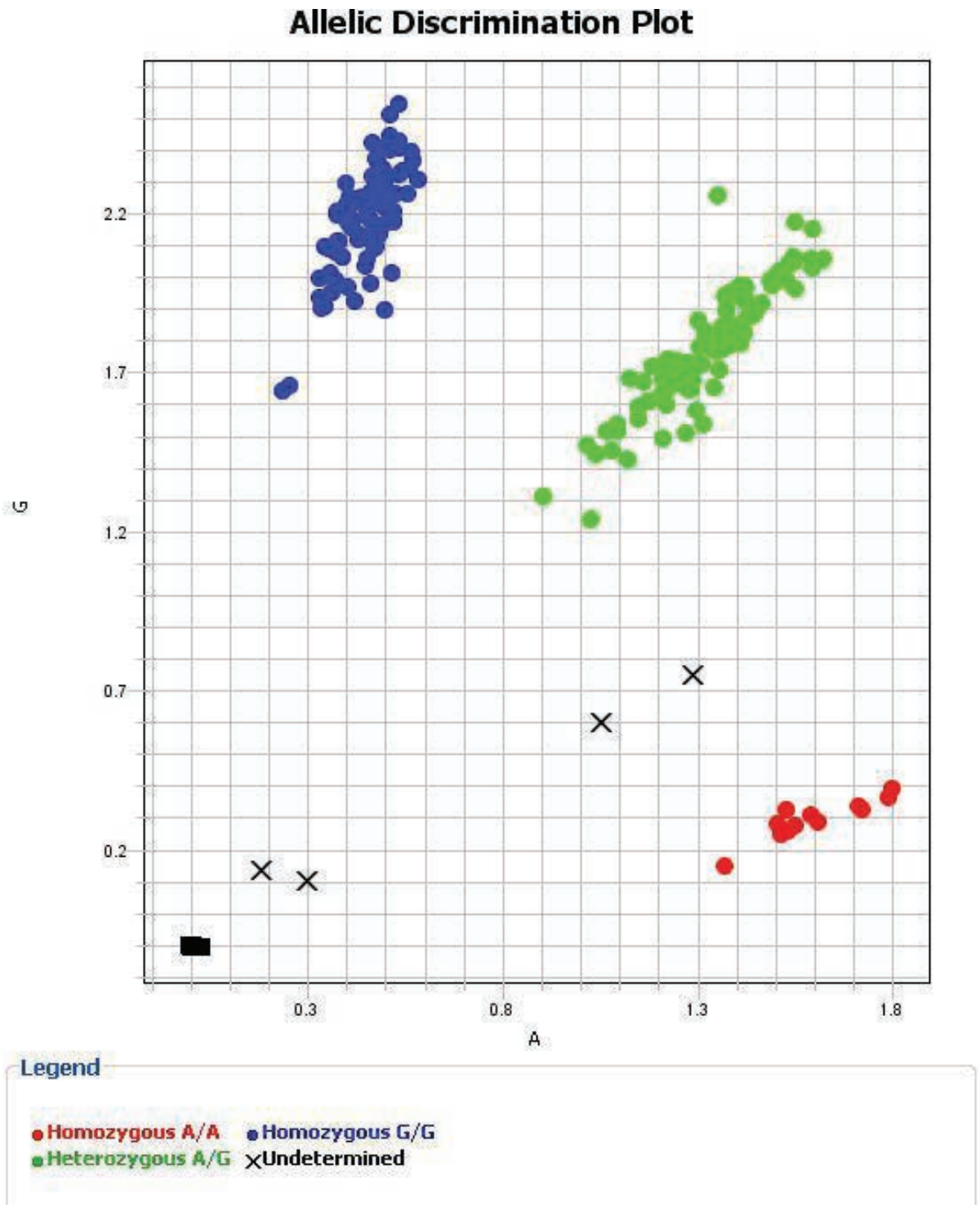
As *COMT* Val/Met variant frequency varies by ethnic group, analysis was restricted to Caucasians

Genotyping for *COMT* rs4680 was done initially in The Applied Genomics Core (SNaPshot), then in the Aitchison lab (TaqMan)

All samples were genotyped in duplicate, for accuracy

100% concordance between methodologies

TaqMan genotyping

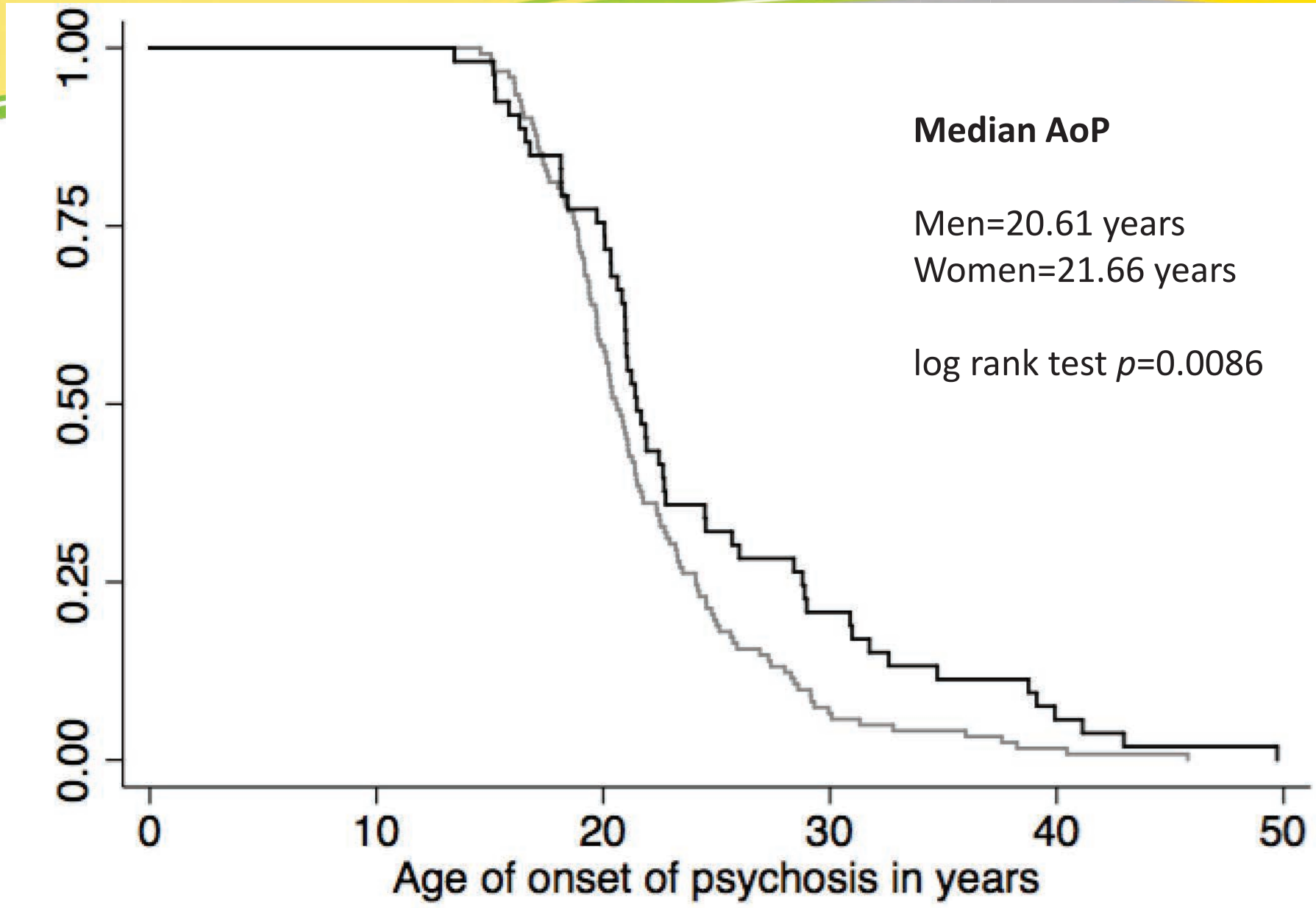


Genotypes were in HWE

Val frequency 0.53

Met frequency 0.47

Men had an earlier age of onset of psychosis (AoP)



Median AoP

Men=20.61 years
Women=21.66 years

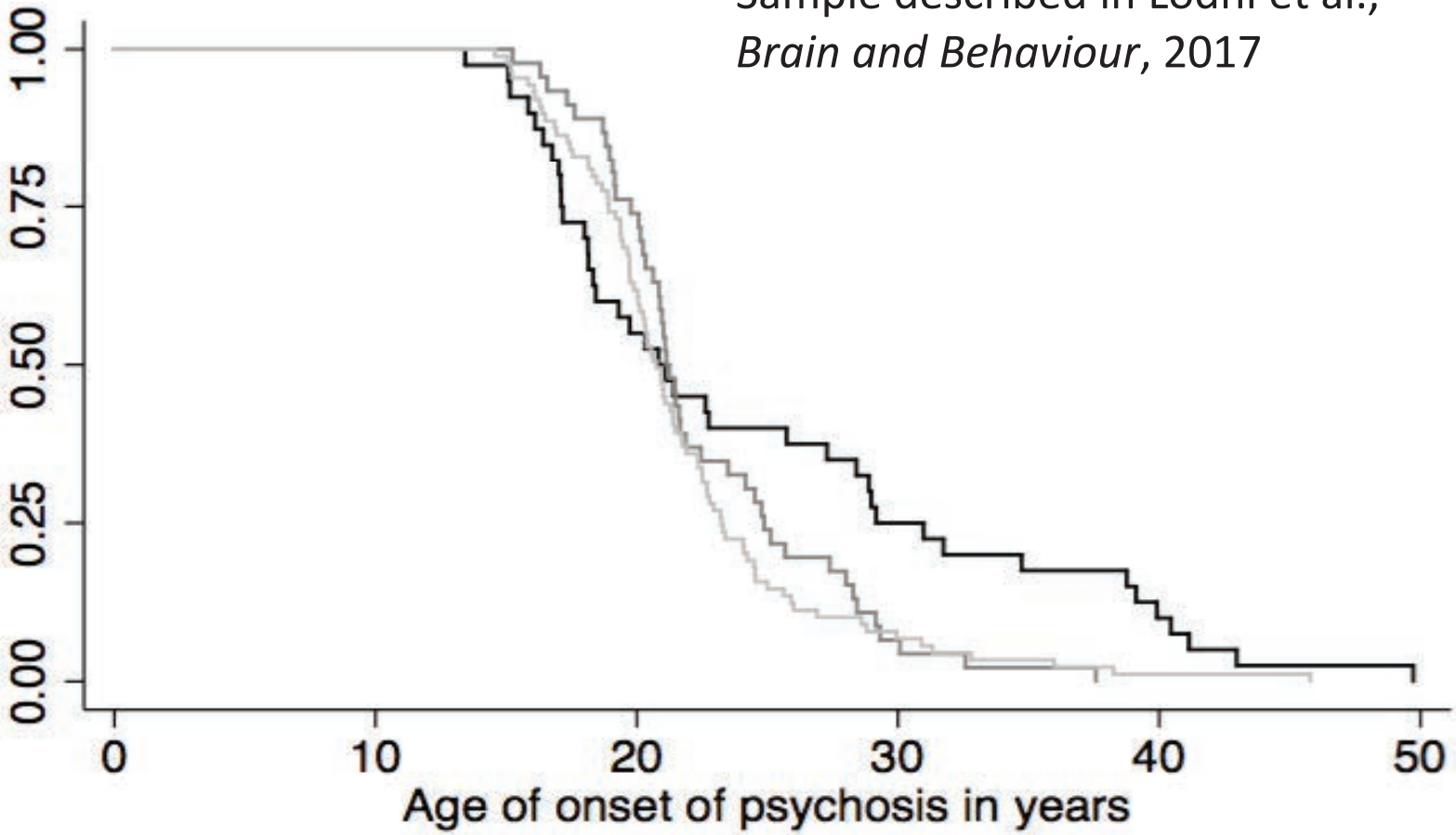
log rank test *p*=0.0086

COMT and lifetime cannabis use

Costas et al. (2011) reported a higher risk of lifetime cannabis use in Spanish COMT Met/Met individuals, who had a diagnosis of schizophrenia

Greater lifetime cannabis use ➔earlier age of onset

Sample described in Lodhi et al., *Brain and Behaviour*, 2017



Number at risk						
LU = 0-9 times	40	40	22	10	4	0
LU = 10-99 times	46	46	34	3	0	0
LU = >100 times	89	89	55	6	1	0

Results

First use of cannabis before 20 y associated with earlier AoP (*p*=0.005)

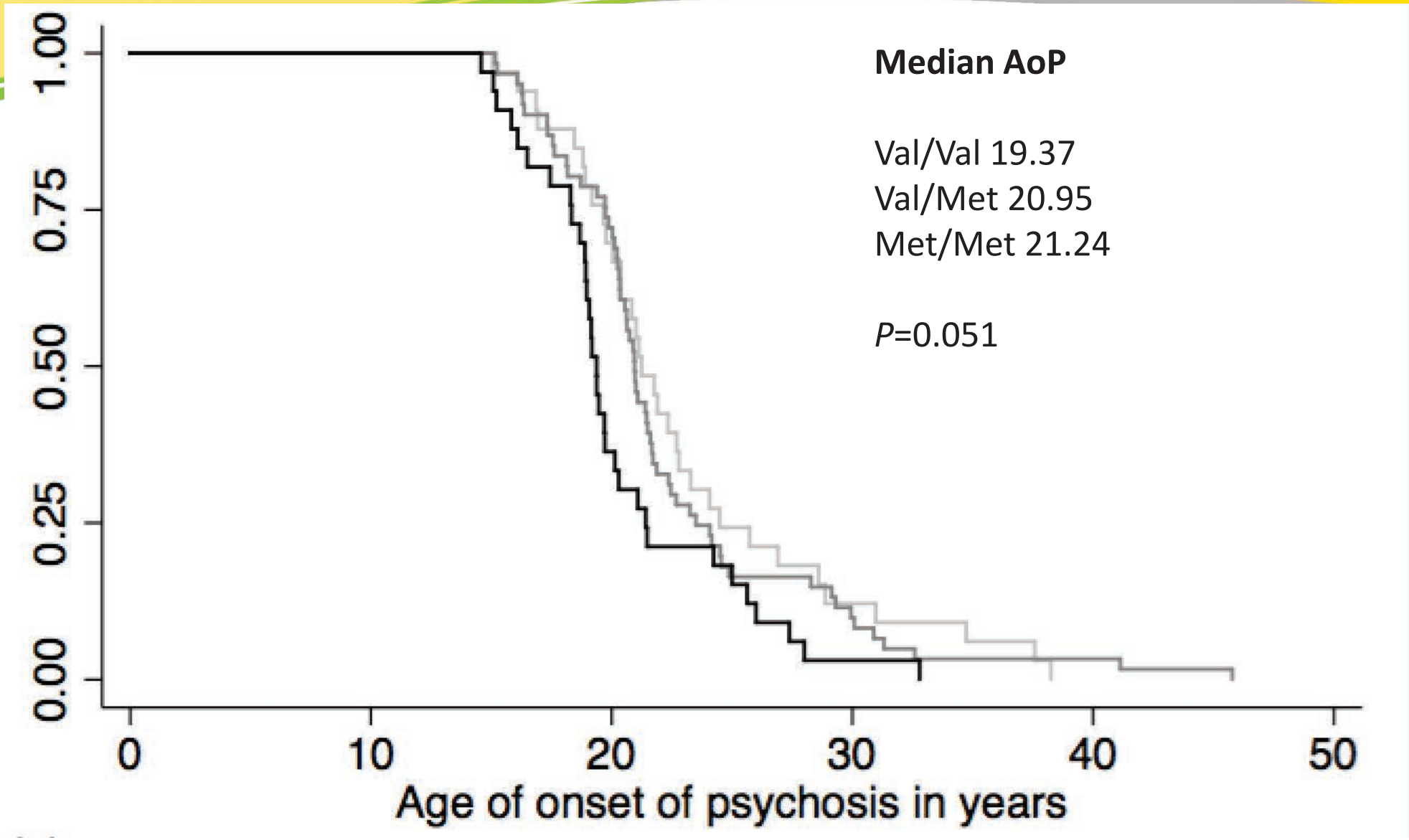
Effect of *COMT* in those first used cannabis before 20 years

- Trend level (*p*=0.051)
  - Remaining on stratifying by gender (*p*=0.079)

***COMT* on AoP was not significant without taking cannabis into account:**

- Val/Val<Val/Met<Met/Met: 21.76, 20.95 and 19.70 years; *p*=0.294

Effect *of COMT* (Val/Val<Val/Met<Met/Met) in first cannabis use <20 years



Median AoP

Val/Val 19.37
Val/Met 20.95
Met/Met 21.24

P=0.051

Conclusions

Trend level signal in the same direction as some previous studies

- **Pattern consistent with an additive effect (Val/Val>Val/Met>Met/Met), consistent with co-dominant pattern previously described**

- **STATA provides the option of statistically testing for the trend of survivor functions: trend of rs4680 on AoP in first cannabis users <20y significant (*p*=0.029)**

Reasons for the consistency between our findings and that of Caspi et al. (2005) may include: diagnostic and ethnic similarities

- **Majority of our patients had a schizophrenia spectrum disorder; Caspi et al. association was with schizophreniform disorder**

- **Ethnicity of Canadians and New Zealanders**

Discussion

- Substance induced psychosis was included; while this may introduce some heterogeneity, there are studies that indicate that primary and drug induced psychosis may be genetically linked
- **Very few of interactions at the molecular-genetic level for candidate genes have been consistently replicated**
- **Replication problems may be due to many factors, including:**
  - **Initial gene selection**
  - **Statistical power**
  - **Bias towards positive results**
- **Increased sample sizes, greater density of genetic markers and a stronger focus on true replication are necessary**
- **However, another gene, which may relate to a common molecular mechanism with *COMT*, shows promising data: *AKT1***

Bramness et al., BMC Psychiatry, 2012

Strengths and limitations

Strengths:

- **Defining psychotic disorder by structured clinical interview (SCID)**
- **Definition of Caucasian ethnicity to the grandparent level**
- With confirmation using markers of known frequencies in Caucasians

Limitations:

- **Sample size and hence subsamples within the sample**
- However, *COMT* analysis in cannabis users before 20 years was sufficiently powered
  - For a one-sided 0.05 level, a 40% reduction in hazard ratio (from our sample for Val/Val group compared to the rest) to achieve power of 0.8, N required = 104
  - 49 volunteers without psychosis, of a similar age but with different gender and cannabis use patterns to the psychosis subjects and with cannabis data were recruited
  - When added the controls, the association between rs4680 and age of onset of psychosis in early cannabis users now reached significance even after adjustment for gender (median AoP: Val/Val < Val/Met < Met/Met 19.37, 21.48, 22.34 y; p=0.0243).
- **The self-report nature of the cannabis use data, & age in ranges**

BDNF, *AKT1*, cannabis, and age of onset of psychosis

BDNF **Val66Met (rs6265) interacts with cannabis use to influence AoP**

- **And it has been reported that gender significantly affects this**

AKT1 **rs2494732 - cannabis interaction on AoP was not previously investigated despite reports of an** ***AKT1*** **effect on risk of psychosis**

Lodhi, Wang et al., in submission

Am J Med Genet B Neuropsychiatr Genet. 2011 Apr;156B(3):363-9. doi: 10.1002/ajmg.b.31174. Epub 2011 Feb 8.

Age at onset of psychotic disorder: cannabis, BDNF Val66Met, and sex-specific models of gene-environment interaction.

Decoster J[1], van Os J, Kenis G, Henquet C, Peuskens J, De Hert M, van Winkel R.

Author information

Abstract

Discovering modifiable predictors for age at onset may help to identify predictors of transition to psychotic disorder in the "at-risk mental state." Inconsistent effects of sex, BDNF Val66Met (rs6265), and cannabis use on age of onset were previously reported. BDNF Val66Met and cannabis use before illness onset were retrospectively assessed in a sample of 585 patients with schizophrenia and their association with age at onset was evaluated. Cannabis use was significantly associated with earlier age at onset of psychotic disorder (AOP; average difference 2.7 years, $P < 0.001$), showing dose-response effects with higher frequency and earlier age at first use. There was a weak association between BDNF Val66Met genotype and AOP (difference 1.2 years; $P = 0.050$). No evidence was found for BDNF × cannabis interaction (interaction $\chi(2)$ (1) = 0.65, $P = 0.420$). However, a significant BDNF × cannabis × sex interaction was found (interaction $\chi(2)$ (1) = 4.99, $P = 0.026$). In female patients, cannabis use was associated with earlier AOP in BDNF Met-carriers (difference 7 years), but not in Val/Val-genotypes. In male patients, cannabis use was associated with earlier AOP irrespective of BDNF Val66Met genotype (difference 1.3 years). BDNF Val66Met genotype in the absence of cannabis use did not influence AOP, neither in female or male patients with psychotic disorder. Complex interactions between cannabis and BDNF may shape age at onset in female individuals at risk of psychotic disorder. No compelling evidence was found that BDNF genotype is associated with age at onset of psychotic disorder in the absence of cannabis use.

AKT1 (rs2494732)

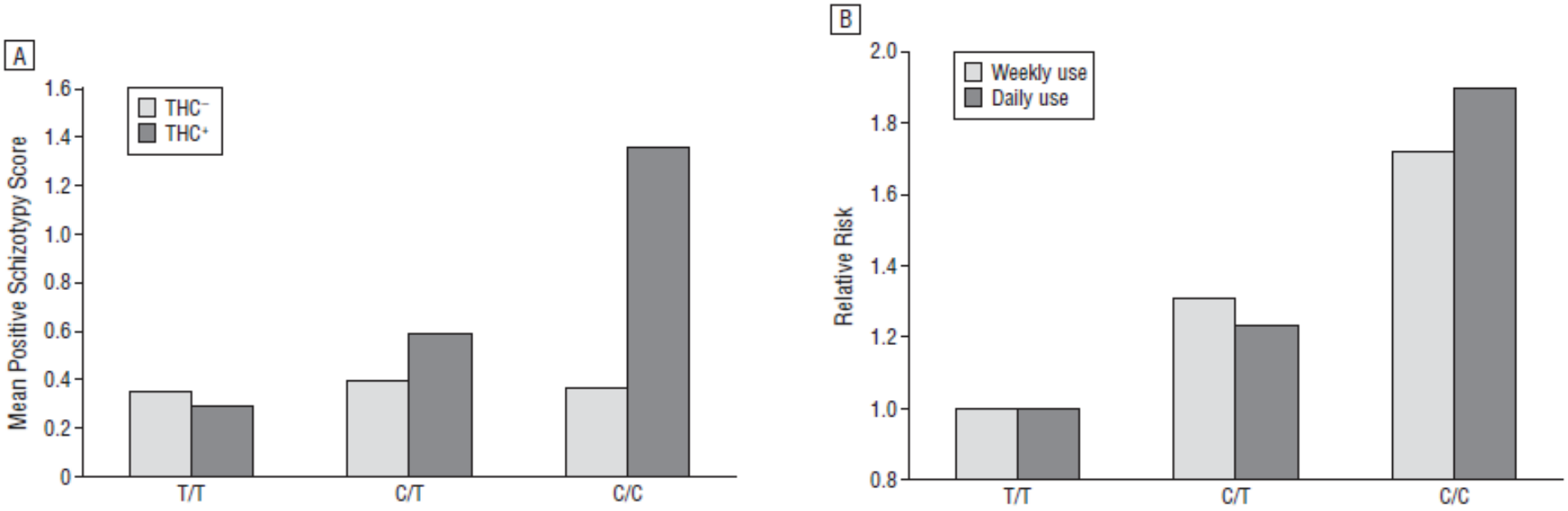


Figure. *AKT1* rs2494732 × cannabis interaction in the at-risk and case-only paradigm. A, Mean positive schizotypy scores according to *AKT1* rs2494732 genotype in 728 unaffected siblings with (n=55) and without (n=673) recent cannabis use. Genotyping was unsuccessful in 12 unaffected siblings. THC indicates tetrahydrocannabinol. B, Relative risks for weekly and daily lifetime cannabis use in the patients according to *AKT1* rs2494732 genotype.

van Winkel (GROUP) 2011, Arch Gen Psych

AKT1 (rs2494732)

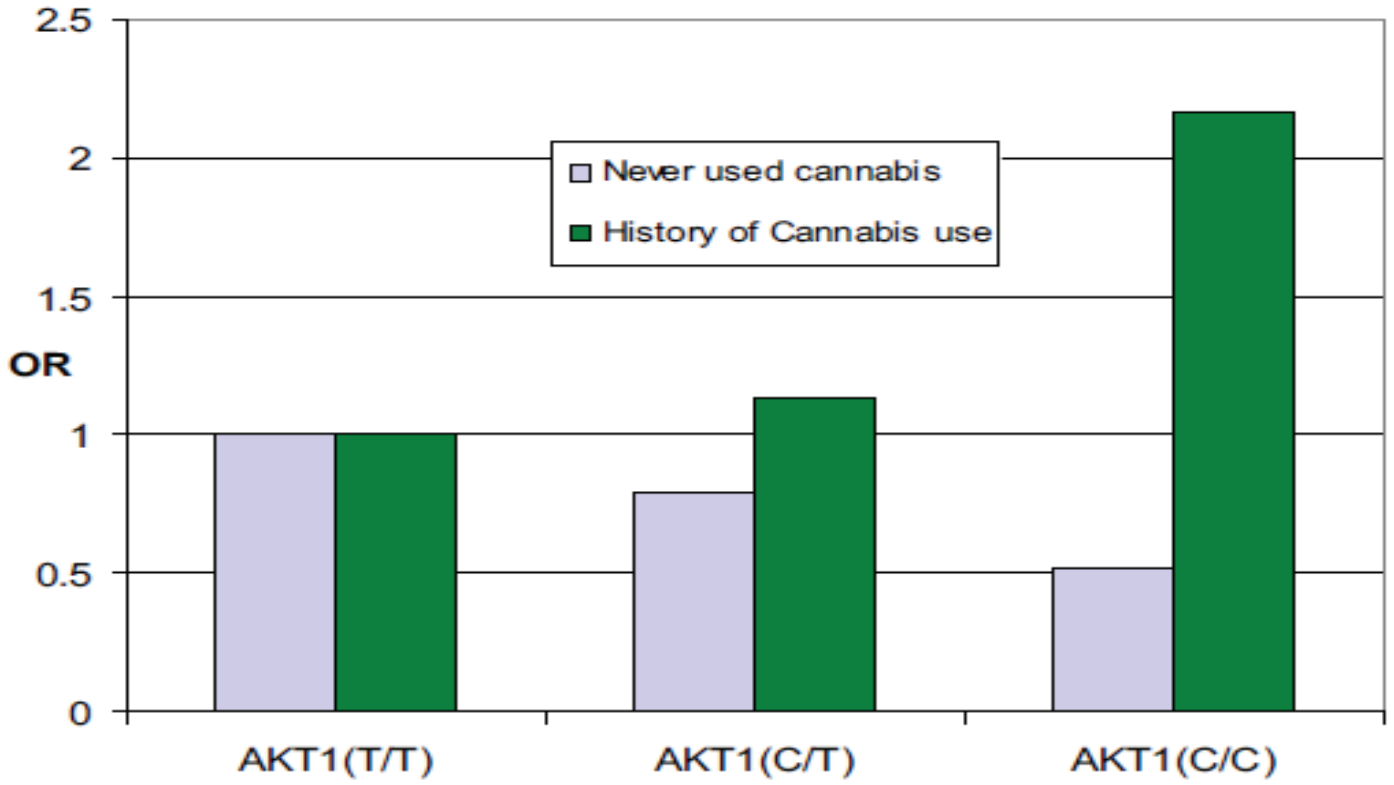


Figure 2. Odds ratio (OR) of psychosis for subjects with *AKT1* rs 2494732 C/T or C/C genotype compared to T/T, according to their cannabis use.

Di Forti et al (2012) *Biol Psychiatry*

Lodhi, Wang et al., in submission

Trend effect for rs6265 – gender interaction (p = 0.067) on AoP, controlling for age at first regular cannabis use

No association was seen between rs2494732 and AoP

- independently
- or in interaction with gender and/or cannabis use

No rs6265 - rs2494732 interaction effect in any of the models.

More studies are required to investigate the role of gender in the rs6265 – cannabis interaction on AoP

Future Directions

- **Independent replication in larger Caucasian samples**
- **If sample sizes permit, include other covariates, such as childhood trauma**
- **Extension to different ethnic groups**
- **Epigenetic analysis**
  - *COMT* promoter methylation has been shown to be associated with frequency of cannabis use in adolescents and young adults.

Public Health Implications

Should there be a public health warning accompanying legalization?

- **Suggest yes, re:**
  - Myocardial infarction, stroke, and cardiac arrythmias
  - Suicidal ideation and behaviours
  - Cancer, especially lung cancer
  - Potential transition to dependence
  - Psychotic illness that may be long-term
  - Long-term neurodevelopmental sequelae

- **How should this be implemented?**

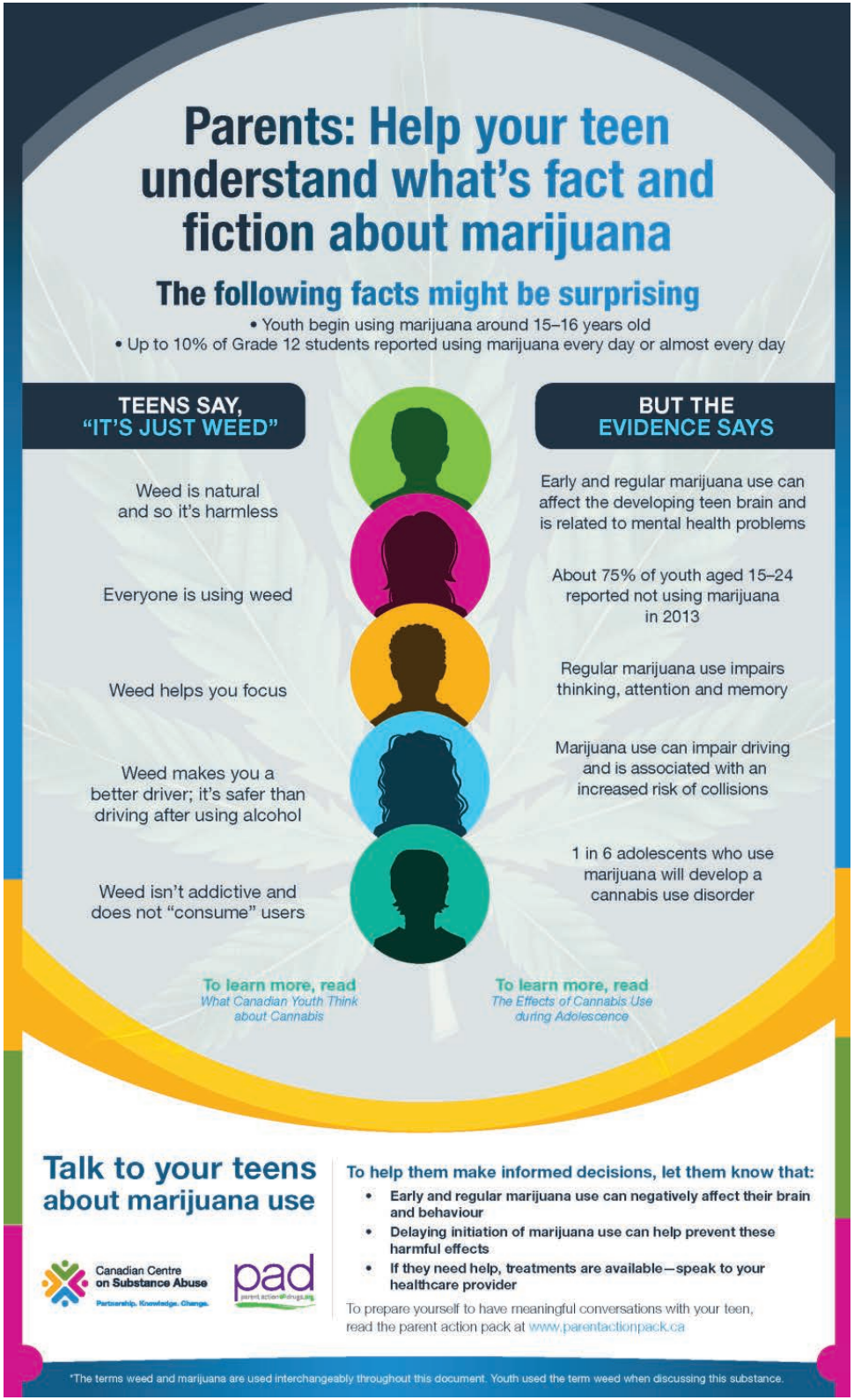
Public Health Implications

Targeted clinical interventions for high risk groups may include:

- *Abstinence* or *harm reduction* from cannabis
  - There is evidence that uptake of such advice could be enhanced by provision of genotype
    - That is, if someone knew they had an at-risk genotype, they would be more likely to abstain
- Healthy lifestyle advice
  - Certain dietary substances may exacerbate risk
- Advice to employ other stress-relieving techniques

And targeted interventions for high-risk groups

- **Young people (<18 y)**
- **The genetically susceptible**
- **Those with childhood trauma**
  - with the possibility that the above variables may be inter-related



http://www.ccsa.ca/Eng/topics/Marijuana/Pages/default.aspx

Canadian Psychiatric Association
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Association des psychiatres du Canada
Dévouée aux soins de qualité

POSITION STATEMENT

Implications of Cannabis Legalization on Youth and Young Adults

Phil Tibbo, MD, FRCPC, FCPA[1]; Candice E. Crocker, MSc, PhD[2]; Raymond W. Lam, MD, FRCPC[3]; Jeff Meyer, MD, PhD, FRCPC[4]; Jitender Sareen, MD, FRCPC[5]; Katherine J. Aitchison, BA (Hons), MA (Oxon), BM BCh, PhD, FRCPsych[6]

A position statement developed by the Canadian Psychiatric Association's Research Committee and approved by the CPA's Board of Directors on February 17, 2017.

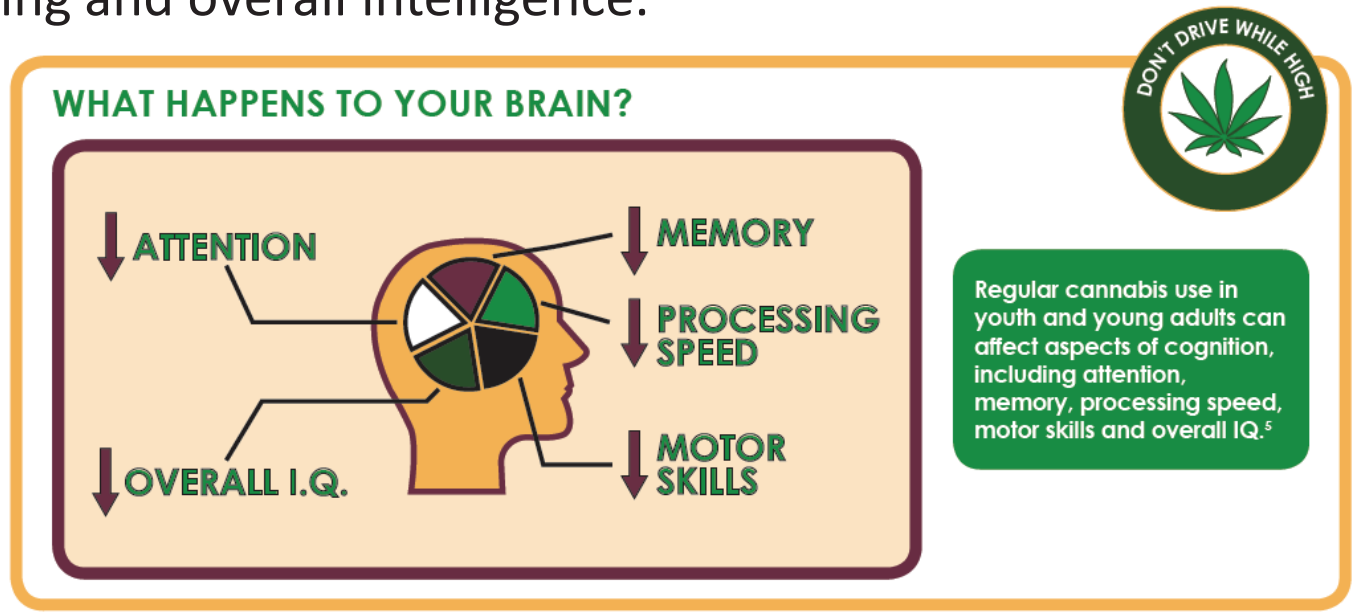
This CPA position statement is focused on youth and young adults as mental illness and substance use disorders often begin in this age group, with the objective to ensure optimal mental health outcomes.

Cannabis is the most commonly used illicit drug for Canadian youth, and Canadian youth are the top users of cannabis in the developed world.

While there are variations by jurisdictions, approximately 22% of youth aged 15 to 19 reported using cannabis during the past year; in this group, 20% report daily or almost daily use.

Image from: Canadian Consortium for Early Intervention Psychosis (CCEIP) Cannabis Use Tear-Pad (EN, 2018) help4psychosis.ca/wp-content/uploads/2018/05/2018-CCEIP-Cannabis-Tear-Pad-EN-pdf.pdf, or mycannabisiq.ca/portfolio/cceip-cannabis-use-tear-pad-en-2018/

Regular cannabis use in youth and young adults can affect aspects of cognition, including attention, memory processing speed, visuospatial functioning and overall intelligence.



Worse performance is related to earlier adolescent onset of use.

Abstinence following regular use may improve some, but not all, of these cognitive domains.

- The human brain undergoes a maturational process during adolescence that includes reorganization, refinements and functional improvements
- This is driven by changes in brain grey matter due to synaptic pruning (elimination of underutilized or unnecessary neural connections), and white matter due to myelination
- These changes continue at least until the mid-20s and thus brain maturation is vulnerable during this time to stressors/insults. The endocannabinoid system plays a role in this brain maturation and thus exogenous cannabinoids from cannabis can affect this process directly in a negative way

Image from: Canadian Consortium for Early Intervention Psychosis (CCEIP) Cannabis Use Tear-Pad (EN, 2018) help4psychosis.ca/wp-content/uploads/2018/05/2018-CCEIP-Cannabis-Tear-Pad-EN-pdf.pdf, or mycannabisiq.ca/portfolio/cceip-cannabis-use-tear-pad-en-2018/

Cannabis Use and mental health disorders

An earlier age of onset of psychosis after adolescent cannabis use has been consistently replicated (reviewed in Hall and Degenhardt 2009, Lodhi et al. 2017).

Since regular cannabis use is associated with increased risk of schizophrenia, and may also negatively interact with depression, bipolar and anxiety disorders due to its biological effects on brain maturation, and since mental disorders frequently start before the age of 25, age of access to cannabis should not be prior to age 21, with restrictions on quantity and THC potency for those between 21 and 25 years of age.

The **course of illness** for non-psychotic bipolar and psychotic illnesses is **worse in the presence of cannabis use**; for example, the mean number of manic, hypomanic and depressive episodes per year is greater in those with bipolar and CUD than in those without (Lagerberg et al., 2014)

Images from: Canadian Consortium for Early Intervention Psychosis (CCEIP) Cannabis Use Tear-Pad (EN, 2018) help4psychosis.ca/wp-content/uploads/2018/05/2018-CCEIP-Cannabis-Tear-Pad-EN-pdf.pdf
mycannabisiq.ca/portfolio/cceip-cannabis-use-tear-pad-en-2018/

Significant support is needed for **public health education** and resources targeting youth and young adults, in collaboration with mental health stakeholder groups.

Significant support of further biological and psychosocial **research** is needed to better understand the impact of cannabis and its legalization on mental health.

Expand support for prevention, early identification and cannabis cessation treatments (i.e., using change- based treatment models including **harm reduction** strategies) within the framework of mental health and addictions.

Prudent consideration of advertising and marketing guidelines with clear markings of THC and cannabidiol content, as well as consistent public health warning messaging, including regarding potential adverse consequences of the use of cannabis during pregnancy, are needed.

CANNABIS: KEEP THIS IN MIND

Image from: Canadian Consortium for Early Intervention Psychosis (CCEIP) Cannabis Use Tear-Pad (EN, 2018) help4psychosis.ca/wp-content/uploads/2018/05/2018-CCEIP-Cannabis-Tear-Pad-EN-pdf.pdf, or mycannabisiq.ca/portfolio/cceip-cannabis-use-tear-pad-en-2018/

CANNABIS: KEEP THIS IN MIND

Image from: Canadian Consortium for Early Intervention Psychosis (CCEIP) Cannabis Use Tear-Pad (EN, 2018) help4psychosis.ca/wp-content/uploads/2018/05/2018-CCEIP-Cannabis-Tear-Pad-EN-pdf.pdf, or mycannabisiq.ca/portfolio/cceip-cannabis-use-tear-pad-en-2018/

https://open.alberta.ca/dataset/0239e5c2-5b48-4e93-9bcc-77f72f7bdc5e/resource/021d8f84-5d8b-4e21- b0bb-81340d407944/download/AHTDP-Cannabis-Evidence-Series-2017.pdf and Lodhi et al., 2017, and review of the literature

EVIDENCE OF HARM

- **Overall: driving (including MVAs), stroke, heart attacks, heart rhythm changes, lung function, drug-drug interactions**

- **Addictions and Mental Health: suicidal ideation, suicide attempts, suicide; earlier age of onset of psychosis and of manic and depressive episodes of bipolar disorder; relapse of a psychotic or manic illness; cannabis use disorder, other substance use disorders; neurological "soft signs"**

- **Cancer: e.g., testicular cancer**

- **Neurocognitive Changes: reduced global functioning, memory, attention and concentration, motivation**
  - **Alterations in dopamine, glutamate, and gamma-aminobutyric acid (GABA)**
- **Harms associated with use during Pregnancy**
  - **e.g., birth complications, low birth weight**

Cancer and MVAs

Marijuana smoke contains high concentrations of the carcinogens found in tobacco smoke (Maertens et al., 2009; Skeldon & Goldenberg, 2014)

Difference in smoking style (larger puffs, longer inhalations compared to tobacco) may ↑carcinogenic risk (Wu et al, 1988)

Second-hand cannabis smoke is more mutagenic and cytotoxic than tobacco smoke (Cone et al., 2011; Maertens et al., 2013; Health Technology Assessment Unit, 2017)

4-8hrs after exposure to second-hand smoke in an unventilated space, levels of cannabis in the blood of 5-10 ng/ml (likely to be associated with impairment, Holitzki, Dowsett, Spackman, Noseworthy, & Clement, 2017); driving offence (~BAC>0.08)

Heart attacks, stroke, and cardiac conduction

Risk of heart attacks is ↑ x 5 within an hour of smoking THC

•And rate of mortality after a stroke or heart attack is elevated in cannabis smokers (Malinowska et al, 2012)

Reports of heart rhythm changes after cannabis include:

•Sinus tachycardia (Jones, 2002), atrial tachyarrythmia (Fisher et al., 2005), paroxysmal atrial fibrillation (Kosior et al., 2000; Kosior et al., 2001; Lehavi et al., 2005), ectopic atrial beats (Fernandez-Fernandez et al., 2011), premature ventricular beats, brugada electrocardiogram pattern (Romero-Puche et al., 2012), asystole (Menahem, 2013), and atrioventricular conduction defects (e.g., second degree A-V block; Akins et al., 1981)

In young people, cannabis use has been associated with an increased occurrence of intracranial arterial stenosis (which can cause stroke; Wolff et al., 2014)

Metabolic syndrome

Abdominal obesity, atherogenic dyslipidemia, high blood pressure, insulin resistance, and proinflammatory and prothrombin states

NCEP-ATP III criteria* provided definitions for the above

International Diabetes Foundation (IDF) differed in their definition and mandated that out of the five criteria, ethnicity adjusted abdominal obesity was necessary

*The National Cholesterol Education Programs Adult Treatment Panel (NCEP-ATP) III, 2001

Harmonized Criteria for Metabolic Syndrome (≥3/5)

Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL (5.6 mM)

HDL-C: high-density lipoprotein cholesterol

Alberti et al. Circulation. 2009;120:1640-1645

Cannabis and obesity: dose relationship

Like the cardiovascular effect of alcohol, there appears to be an inverted U-shape

Compared to non-users (Huang et al, 2013)

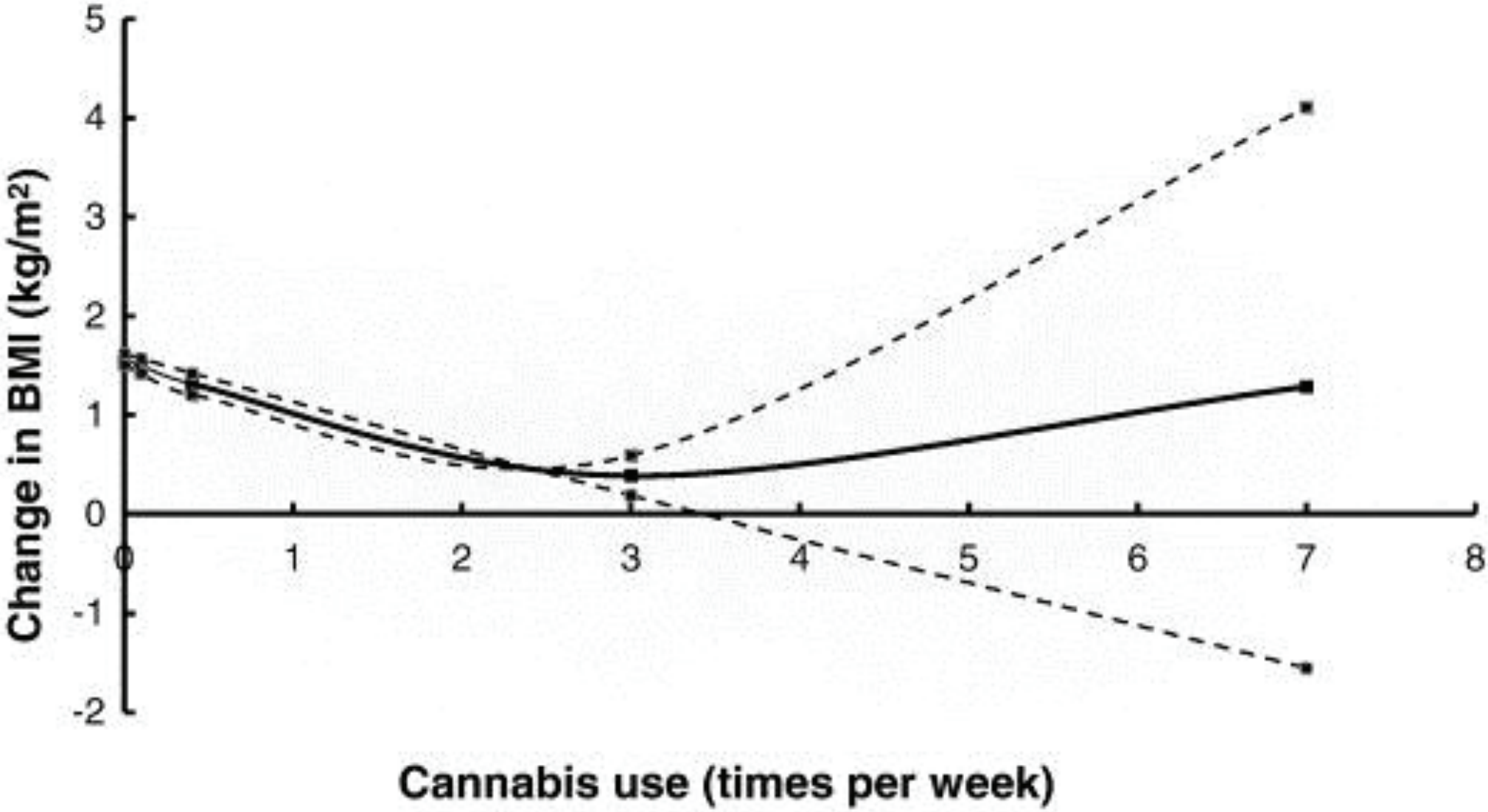
- **Adolescents with high cannabis use ↑ risk adult obesity as adults**
- **Adolescents who used sporadically ↓ adult obesity**

This effect was replicated in females by Dubé et al (2015), who also found that cigarette smoking modified this association in males

- **Inverted U seen only in non-smokers (~0.5 cigarettes/day)**

Dubé et al (2015)

Change in BMI (kg/m2) in females by cannabis use

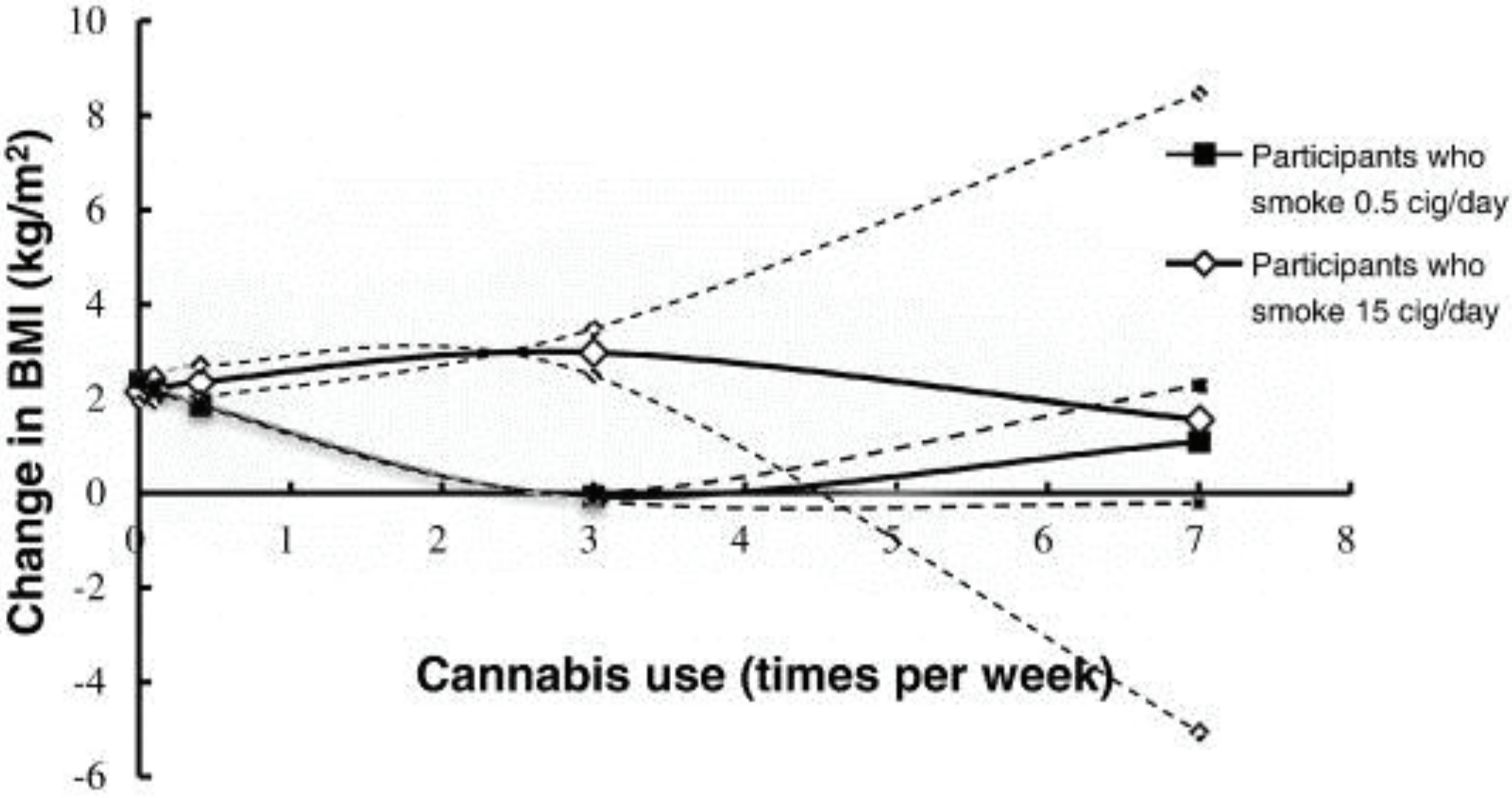


Note: Model adjusted for baseline BMI, physical activity, smoking and sedentary behavior. Dashed lines indicate 95% confidence interval.

http://dx.doi.org/10.1016/j.pbb.2015.04.018

Dubé et al (2015)

Change in BMI (kg/m2) in males is moderated by cigarette smoking



Note: Models adjusted for baseline BMI, physical activity, sedentary behavior and alcohol consumption. Dashed lines indicate 95% confidence interval.

http://dx.doi.org/10.1016/j.pbb.2015.04.018

Cannabis and blood pressure

The most consistent cardiovascular effect of THC is a dose-dependent increase in heart rate (Zuurman et al, 2009)

There is an acute dose-dependent increase in blood pressure and heart rate, along with orthostatic hypotension, after THC use (Jones et al, 2002; Heishman et al, 1989)

- For orthostatic hypotension, those with a higher baseline BP may be more affected

However, tolerance to these effects develops after a day or two of repeated use (Jones et al, 2002; Benowitz & Jones, 1985)

- And tolerance is lost rapidly on cessation of use (Benowitz & Jones, 1981)

Chronic use may in fact be protective against hypertension (Moore et al, 2012)

Cannabis and blood pressure (continued)

Cardiovascular effects appear to vary by the type of cannabinoid

- **Tetrahydrocannbinol (THC, exogenous): biphasic effects on BP**
- **Anandamine (endogenous) may have triphasic effects (Malinowska et al, 2012)**

Cannabis and glaucoma: ↓ blood pressure (BP) precedes a ↓ in intra-ocular pressure (Merritt et al, 1980)

Discussion

Although there may be some positive effects of a low dose of cannabis on obesity, BP and diabetes

- **With data mainly from general population**

The increased risk of *MI, CVA and mortality* associated therewith are *major concerns*

In addition, cannabis has a different effect on the endocannabinoid system in patients with and without psychosis

- **Frequent use of cannabis is associated with down-regulation of the endogenous cannabinoid, anandamide, in CSF**
  - **only in patients with schizophrenia and not in healthy controls**

Given the above and the increased risk of MI, CVA, and mortality associated therewith (which is already substantially above the general population), in those with a vulnerability to psychosis, THC is likely to be associated with deleterious cardiovascular effects

Lung conditions in general

"individuals should be advised that smoking cannabis might lead to serious short-term or long-term respiratory complications that are potentially as serious as those from tobacco smoke"

(Lutchmansingh et al, 2014)

Testicular cancer

Association with testicular germ cell tumours (especially non-seminoma tumours; meta-analyses; Gurney et al, 2015; Huang et al, 2015)

- Current, long-term, early exposure (<18 years), and/or frequent cannabis use compared to never users

Summary regarding risk of cancer

With smoking route

Dose-response relationship

- **Earlier age of exposure increases risk**
- **More frequent use increases risk**

Synergistic effect with tobacco smoke possible

- via common pathways, including polymorphic enzyme mechanisms

Funding includes

Bebensee Schizophrenia Research Unit (Director SE Purdon).

CIHR grant (200810): NPAS3 variants in schizophrenia. D Cox, with S Purdon and P Tibbo. Grant latterly held by K Todd.

NPAS3 variants in schizophrenia: A neuroimaging study. Nova Scotia Health Research Foundation (NSHRF) 2012-13 Establishment Grant to Tibbo P. Co-Investigators: Rusak B, McAllidon D, Bernier D, MacIntyre G, Bartha R, Purdon SE, Beyea S, Song X, Aitchison KJ. $150,000 over 3 years (Sept 2012-Sept 2015).

Canadian Foundation for Innovation (CFI), John R. Evans Leaders Fund (JELF). Pharmacogenetic translational biomarker discovery. Aitchison KJ (PI), Halloran P, Sommerville M (Co-Applicants). $694,961 over 5 years (November 2013-October 2018).

Alberta Innovation and Advanced Education (IAE). Aitchison KJ $ 277,985 over 5 years (December 2012-October 2017).

Government of Alberta: Alberta Centennial Addiction and Mental Health Research Chair to Aitchison, KJ (Sept 2011~Dec 2016) $1,250,000

www.epicanada.org / www.ippcanada.org

The Canadian Consortium for Early Intervention in Psychosis (CCEIP)

National, not-for-profit organization of clinicians and researchers dedicated to improving the quality of care for individuals in early phase psychosis.

VISION: Towards a healthy future for Canadians in the early phase of psychosis.

MISSION: To enhance optimum care for Canadians in the early phase of psychosis through improved service models and the generation and translation of knowledge.

CCEIP Membership

National and bilingual organization of clinicians and researchers who are associated with early psychosis programs.

CCEIP Objectives

1. Effective advocacy for service development, implementation and improvement
2. Clinical research across the spectrum of biological, psychological and social determinants of illness, interventions, and studies of service delivery models to influence mental health policy based on evidence
3. Training across programs for clinicians, researchers and trainees from all disciplines
4. Development of standards for service delivery

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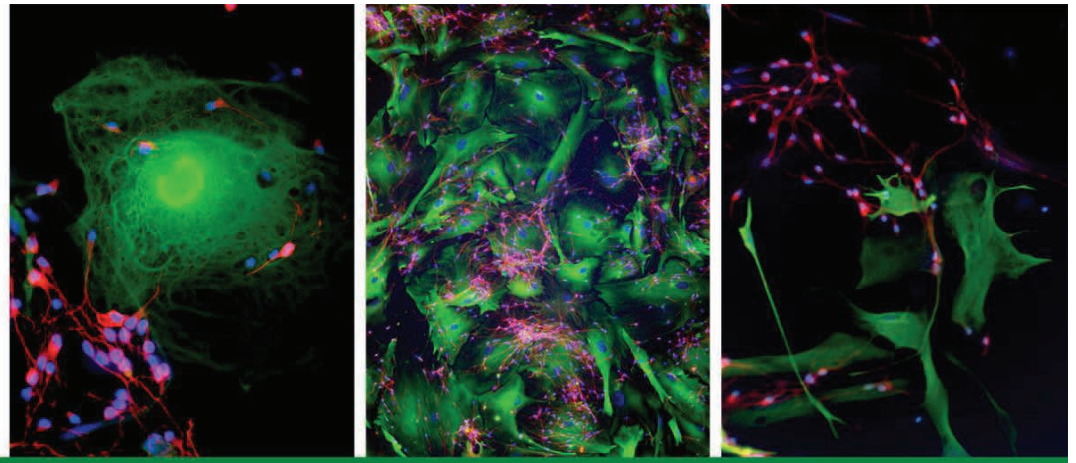

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"uplifting the whole people"

— HENRY MARSHALL TORY, FOUNDING PRESIDENT, 1908